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PHYSIOLOGICAL REVIEWS

VOL. IX APRIL, 1929 No. 2

THE SUSPENSION STABILITY OF THE BLOOD

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During the last decade more and more attention has been paid—in Scandinavia and Germany in particular—to a new clinical form of examination of the blood, namely, the determination of the sedimentation velocity of the red blood corpuscles, or, in terms of colloid chemistry, the determination of the suspension stability of the blood.

HISTORICAL REVIEW (1, pp. 3–69). After a break of nearly 100 years, the study of a problem that has played a unique part in the earlier history of medicine has thereby been resumed. That such was the case is explained by the fact that no other reaction of the organism in disease exists that affects the appearance of drawn blood in such a conspicuous manner as an increased sinking velocity of the red corpuscles. For in most diseases this velocity is so strongly increased that the red corpuscles, situated in the uppermost layer of the blood, have time to form a sediment before the plasma coagulates. As a consequence the upper portion of the blood-clot comes to consist of a more or less thick fibrinous layer, which does not form in the blood of a healthy person, in whom the corpuscles sink comparatively slowly. The appearance of this fibrinous layer was not merely interpreted as a symptom of disease; it was considered that the substance of which it was made up constituted the injurious matter which, having been aggregated in the vascular system, represented the true cause of the disease.

According to the pathology of antiquity, as expounded by Hippocrates and Galen, health was conceived as dependent upon the normal mixture of the four fluids which were believed to compose the vascular contents, thus forming what we call blood. As is well known, these four fluids were: the yellow bile, *cholera*—the serum which separates from the blood-clot; the black bile, *melancholia*, seemingly collecting as a dark colored substance in the lowermost portion of the blood-clot; blood in the restricted sense of the word, *sanguis*, the upper bright red portion

of the blood-clot in contact with the air (the black bile and the "blood" thus corresponding to the red corpuscles); and the mucus or *phlegma*, answering to what we now call fibrin. From a theoretical point of view, disease might arise as a result of the increase of any of the four fluids, but in reality the accumulation of the phlegma in the vascular contents was thought to be by far the most important cause of almost all diseases. The principal reason for this was the above-mentioned observation that blood drawn from most diseased persons was found covered with a fibrinous layer—a fact which the Hellenic physicians naturally thought to be a consequence of the phlegma having unduly increased in the vascular system. Moreover it was known at that time that the clotting of blood depends on the coagulation of the phlegma—a process which was considered to take place in the organism when this fluid had accumulated in the vessels, thereby giving rise to formations which we should call thrombi.

This view was substantially supported by the fact that well-marked so-called fibrin coagula, arising post mortem in the heart and in the large vessels in a perfectly analogous manner to the above-mentioned fibrinous layer in drawn blood, are found at autopsy of persons who have died from disease, being absent on the other hand in cases of violent death.

The downfall of the antique four-fluid theory in modern times did not, as a matter of fact, d minish the importance of the fibrinous layer. In the literature of the 17th, 18th and 19th centuries, this formation is known under many names such as crusta inflammatoria, phlogistica, pleuritica—couenne du sang—buffy coat—Faserstoffhaut, Speckhaut. Thus altered, the blood was called buffy or sizy, the Germans named it "zerfallenes Blut."

The Greeks were right when they believed that the clotting of blood depended on coagulation of the phlegma; the old physicians of later times were wrong when they thought that clotting was due to the clustering of the red corpuscles. The existence of these formations having been demonstrated by aid of the microscope, the blood was considered to consist of only two main constituents, namely, the red cells and what we now call serum. The consequence of this oversight was that the fibrin collecting at the top of blood drawn from diseased individuals was interpreted as a substance entirely alien to the composition of normal blood, the presence of which was thought to explain the most varied clincial symptoms, as fever, perspiration, eruption on the skin and so forth. The buffy coat was as a matter of fact the salient point in the general pathology of the clinical leaders of that time. Sydenham (60),

for instance, believed the common cause of all febrile diseases to be an inflammation of the blood, the pathognomonic sign of which was the *size.* Boerhaave (10) thought that all disturbances of the circulation in disease were due to the same substance lodging in the narrow vessels.

To give only an idea of the significant bearing of these observations on the treatment of disease, it may be mentioned that the theoretical argument in favour of venesection—the supreme method of treatment for thousands of years of medicine—was founded on the conception that by emptying the vessels of their contents the organism could be relieved more or less from the *materia morbificans,* i.e., the substance of the buffy coat.

As will be seen by the following, the sedimentation velocity of the red corpuscles is increased during one physiological condition, namely, pregnancy. Pregnant women had buffy blood and were therefore victims to blood-letting in a formidable degree, a procedure still in use at the beginning of the last century.

As the conception of the humoral causes of disease was supplanted by the cellular pathology of Virchow, the changes in the blood were relegated to the background, and after a few decades the existence of the crusta inflammatoria was completely forgotten—a fact to which the discontinuance of venesection naturally contributed.

Prior to this, however, considerable advance had been made in the scientific study of the sizy blood and its nearest causes. For the first time it was pointed out by the early deceased English physician, William Hewson (1772) (23, pp. 1–90), that "The inflammatory crust or size is not a new-formed substance, but is merely the coagulable lymph separated from the rest of the blood," and further this eminent hematologist gave utterance to the opinion, that of the two circumstances which separately or together could give rise to the size, namely, delayed coagulation or increased sedimentation velocity, the latter factor had by far the greater influence.

Light had also been thrown on the question why the sinking velocity of the red corpuscles was increased. In his lectures during the year 1786, John Hunter (26, I p. 235) described pathological blood in the following manner: "In all inflammatory dispositions in the solids, whether universal or local, the blood has an increased disposition to separate into its component parts, the red globules become less uniformly diffused, and their attraction to one another becomes stronger, so that the blood when out of the vessels soon becomes cloudy or muddy and dusky in its colour, and when spread over any surface it appears mottled, the red blood attracting itself and forming spots of red."

The most exhaustive inquiry into the causation between sizy blood, sedimentation velocity and aggregation of the red corpuscles is however due to the German investigator Hermann Nasse (1836) in his extensive hematological work, *Das Blut* (42), in which hundreds of pages refer solely to the problem of the buffy coat. In an excellent manner he here proves that the buffy coat as a rule owes its origin to an increased sinking velocity of the red corpuscles, and that, furthermore, this phenomenon must have something to do with the peculiar clustering tendency of the red corpuscles. He says: "So wenig man nun einen directen Einfluss der spezifischen Schwere der Blutkörperchen anzunehmen geneigt sein kann, so wenig ist ein indirecter, bisher von niemand anerkannter zu läugnen. Bei der mikroskopischen Untersuchung des Blutes hatte ich gefunden, dass die Körnchen je mehr sich ihrer verbinden, desto schneller zu Boden sinken und das ganz besonders in dem faserhäutigen Blute die Neigung sich zu vereinigen auffallend gross ist, so wohl in dem frischen als in dem geschlagenen."

The parallelism between the sedimentation velocity of the corpuscles and their degree of clustering was somewhat later pointed out by Jones (1843) (27) who states, like Hunter, that in order to know if a patient's blood has a buffy tendency or not, it is sufficient to take a drop of blood from the finger tip, press it between two pieces of glass and observe whether or not it shows a dotted appearance. And just as there are differences in the degree to which the buffy coat is developed, corresponding degrees may be distinguished by the distinctness with which these dots make their appearance.

The aggregation of the corpuscles being the essential property of buffy blood, gave, as especially Gulliver (1845) (19) found out, the explanation of a peculiar observation which had been known for a long time. Since Harvey's days at least, it was a well established fact that the blood of even healthy horses had a strong tendency to become buffy. The sinking velocity of the corpuscles in horses' blood is much greater than in that of all other healthy animals, and there exists here a physiological aggregation of these cells, which is so strongly pronounced that it can only be compared with the aggregation occurring in human beings during serious diseases.

At this time, however, the research work upon the causes of the buffy blood had also taken another line, which is of great interest for the modern treatment of the problem.

The first quantitative analysis of the blood, made 100 years ago, concerned the fibrin. Scudamore (53) and the leading French hematolo-

gists, Andral and Gavarret (4), found that this constituent of the blood was, as a rule, several times increased in sizy blood, but for divers reasons this fact was not associated with the increased aggregation of the red corpuscles.

On the other hand, Hewson had already made observations which he himself thought to be proof of the fact that the fibrin in some way furthered the sinkng velocity of the red corpuscles. He found the paradoxical condition that the red corpuscles settle very much more slowly in defibrinated blood than in whole blood, where the fibrin is still dissolved in the serum. This fact was later verified by the great German physiologist, Johannes Müller (1833) (40) who, examining the causes of the buffy coat, attributed to the quantity of fibrin a determinative influence on the development of this phenomenon.

As late as the first half of the 19th century, the buffy coat formed one of the questions most written about. As an example, the French scientist Denis, in his monograph on the chemistry of the blood (1838) may be cited (14): "Dans tous les temps, la formation de ce qu' on a appelé la couenne du sang a été expliquée de beaucoup de manières. On a publié sur elle une foule d'écrits. Il se passe même peu d'années sans qu'il paraisse un travail qui la concerne. Mais autant d'explorateurs, autant d'opinions. Un tel état d'incertitude, sur un sujet qui pique vivement la curiosité, l'importance qu'on paraît attacher à la modification qu'éprouve alors le sang, et les inductions patologiques et therapeutiques qu'on a voulu en tirer, m'ont fait porter mon attention sur l'état couenneux avant tout autre état morbide."

At this period study of the problem—without doubt the most significant in the hematology of that time—was discontinued and the results already gained were entirely forgotten.

It should be added that Biernacki—evidently without knowledge of the older literature—in the nineties published several essays (9) on the sedimentation of the red corpuscles, which process he ascribed to the secretion of plasma by the red cells. He adopted the peculiar conception that the greater part of the plasma was squeezed out from the corpuscles in dying blood, a process which took place with various degrees of speed in different cases. His observations, however, were never accepted, probably owing to the absurd theoretical explanation advanced.

In this brief historical review it may finally be noted that the increased aggregation of the red corpuscles in fresh blood specimens in cases of more severe inflammatory conditions was recognized by French hematologists (20, 8), in particular, at the beginning of this century.

The publications of the present author which originated from accidental observations (1917) on the increased sedimentation velocity of the red corpuscles during pregnancy, have renewed interest in these hematologic questions and during the last decade thousands of papers concerning the sinking speed of the erythrocytes have been published. Most of these publications, however, only bear upon the clinical importance of this phenomenon and can not be reported in this review which chiefly aims to give a short account of the physical and physiological side of the suspension stability of the blood.

METHODS. The buffy coat may be considered only as an historical phenomenon without bearing upon modern clinical work. Phlebotomia nowadays has comparatively limited scope and the large blood specimens required to demonstrate the buffy coat are seldom available. And, moreover, the appearance of the drawn blood—if sizy or not—is, as already mentioned, dependent not only upon the tendency of the red corpuscles to sink fast or slowly, but also upon the time of coagulation of the blood. The modern technique eliminates the influence of the last-named factor by studying the sinking velocity of the red cells in blood which has been prevented from coagulating.

For the latter purpose a number of different methods have been suggested in recent years, of which the one proposed by Westergren (2) is probably the best and most used. Although it requires venous puncture, it is done with a very small quantity of blood and is undoubtedly to be preferred to the micro-methods in which only a drop of so-called capillary blood is used.

To prevent coagulation, a 3.7 per cent solution of sodium-citrate is mixed with the blood in a proportion of 1 to 4. A syringe holding 1 cc. is first filled to one-fifth of its capacity with the sodium-citrate solution and the blood is then drawn up to fill it completely. It is of advantage in a large series of examinations to have the barrel supplied with a catch so as automatically to give the correct quantity of citrate solution. The contents of the syringe are transferred to a small test-tube and mixed by shaking. The citrate blood is then sucked up into a pipette-like glass-tube of an inner diameter of about 2.5 mm. to a height of 200 mm. The tube so filled is then placed vertically in a stand of special construction and there fixed by means of a spring, which is brought down on the top of the tube and presses its tip against a rubber cork attached to the bottom of the stand.

The sedimentation velocity is now obtained by measuring the distance passed by the uppermost layer of the red corpuscles from the upper

meniscus of the fluid column in a given time. The boundary between clear plasma and red corpuscles is generally perfectly sharp. The time after which the reading should be made may be open to discussion, for the speed with which the red corpuscles sink varies for different phases of the sinking process. As will be clearly seen from the following, the sedimentation rate is a function of the degree of aggregation of the red corpuscles. It takes, however, a certain time—in blood of strong aggregation tendency about 5 minutes, in blood where this tendency is weak about 25 minutes—before the aggregates have obtained their definite size (and density). Therefore the sinking velocity is relatively small at the beginning of the sedimentation process, but increases steadily to attain after these intervals a constant value which is not thereafter altered. Because of the fact that the red corpuscles gradually begin to pile up on the bottom of the tube, we sooner or later get a slowing down of the sedimentation process also of the uppermost corpuscle-layer. It is clear that the sinking velocity, which corresponds to the size of the completed aggregations, is really only to be found during the intermediate phase of the sedimentation. This value is easily found by reading off at different times and graphically registering the results. The inconvenience of several readings, however, gives no corresponding gain from a clinical point of view. One reading is sufficient and this ought to be made after one hour. In the course of this time the sinking has at any rate proceeded so far as to yield readable values, but has not, as a rule,—even in samples of the most rapid sedimentation—had sufficient time to be completed It must be emphasized that all high figures for sedimentation velocity—above about 60 mm. per hour—become lower than what corresponds to the existing aggregate formation. A value of 100 mm. per hour, corresponds thus to a value of about 200 mm. or more, had we used tubes of sufficient length. But from a clinical point of view, it is fairly unimportant whether the highest grades of aggregate formation are represented by relatively too low velocity figures.

A blood examination thus carried out with a determination in millimeters of the distance passed during one hour of the uppermost corpuscle-layer, is called a stability or sedimentation reaction.

It may be mentioned that many other modifications of my original method for the sedimentation velocity have been proposed. Linzenmeier (33) and others take the time in minutes required for the corpuscles to sink a certain distance marked on the tube. Berczeller and Wastl (7) and Lundgren (36) have suggested the use of inclined tubes, in which

the sedimentation is hastened because of the fact that the red corpuscles sink to the lower side of the tube and form a coherent stream, a coherent plasma stream contemporaneously going upwards along the upper side of the tube. For further particulars about different techniques, see Westergren (2) and Katz and Leffkowitz (3).

CLINICAL SIGNIFICANCE OF THE STABILITY REACTION. The sedimentation velocity of the red corpuscles in man is subjected to physiological variations according to age, sex, and in woman to the presence or absence of pregnancy.

The lowest figures are obtained in the newborn (average 0.5 mm.). In adults, men generally show considerably lower figures (as a rule 1 to 3 mm.) than women (as a rule 4 to 7 mm.). Of practical importance is the upper limit of the figures that may be considered as normal. I formerly held (1, p. 78) this limit in men and women to be 10 and 13 mm. respectively. But more experience with the reaction leads me to believe that these figures may be too high for perfectly normal individuals.

During pregnancy the sinking velocity is increased beyond the normal. This increase is already apparent in the second month of pregnancy and reaches its highest figures at the end of the term, subsequently receding rapidly during the puerperium. The following table shows the average sinking velocity in 100 women during different periods of gestation (1, p. 77).

Month of pregnancy	*mm.*	*Month of puerperium*	*mm.*
2nd	17	1st	41
3rd	24	2nd	20
4th	20		
5th	29		
6th	33		
7th	40		
8th	47		
9th	45		

In a very great number of diseases, the sinking velocity is increased in most cases very considerably above the normal. A sinking velocity of 30 mm. and above may be considered as a very marked reaction, but in many diseases, such as sepsis, pneumonia and acute polyarthritis, the figures are regularly raised to about 100 and beyond.

The sinking velocity is more or less increased in all acute general infections, and is of particular value here as a source of information as to the occurrence of complications; conditions such as pleurisy, otitis and others being generally accompanied by still higher figures. In case of

uncomplicated influenza, for example, the normal value is only slightly raised, whereas, if septic complications arise, the sinking velocity becomes greatly increased.

In the chronic infectious diseases, syphilis and tuberculosis, the sinking velocity is as a rule fairly markedly increased. The province of internal medicine, in which the practical use of the stability reaction has been most fully worked out and the most important results obtained, is probably pulmonary tuberculosis. As was first found by Westergren (2), and since confirmed by a great many investigators, the sinking velocity may be said, on the whole, to reflect better than the body temperature the intensity of the tubercular process. A high sinking velocity is a bad prognostic sign, whereas a low velocity, even where pulmonary and general symptoms are in other respects prominent, is, as a rule, strongly in favour of a good prognosis.

In other pulmonary diseases of more severe nature, there is as a rule a very marked sinking velocity. Croupous pneumonia, for example, as already mentioned, is productive of some of the highest figures known. In this condition the sinking velocity in a previously healthy person may rise a hundredfold within the course of a day or two.

In the local inflammatory conditions of surgery, gynecology and orthopedics, the sinking velocity has been extensively tested and by most observers has been deemed of decided importance for estimating the intensity of the local infection, and, on that account, has proved of valuable aid in treatment.

Malignant tumours—at least in an advanced stage—generally show a considerably increased sinking velocity, the explanation being probably found partly in influence of the tumorous tissue itself, partly in intercurrent infections.

Generally speaking, it may be said that a reduction of the suspension stability of the blood is one of the most common general reactions of the organism in disease, perhaps the most common. In this respect it may best be compared with such reactions as pyrexia and leucocytosis. The increased sinking velocity has many features in common with these phenomena without running parallel to either of them. It occupies, therefore, an entirely independent position in clinical symptomatology. On account of its completely non-specific character, the reaction has, as a rule, proved less instructive in respect to the diagnosis of the disease, than as regards the activity or intensity of the morbid process. Good surveys of the clinical significance of the stability reaction have been published by Westergren (2) and Katz and Leffkowitz (3).

HYDRODYNAMICS OF THE SEDIMENTATION (1, pp. 92–114). A spherical particle suspended in a fluid of less specific gravity than the particle itself, is attracted to the earth by a force equal to: $\frac{4}{3}\pi r^3 (S-S_1) \cdot g$. In this formula r stands for the radius of the sphere, S for its specific gravity, S_1 for the specific gravity of the fluid, while g is the gravitation constant. As found by Stokes (59), the fluid offers a resistance to the movement of the sphere equal to $6\pi r v \mu$, where v denotes the velocity of the movement and μ stands for the absolute viscosity of the fluid. The movement of the sphere is at first accelerated, but becomes constant from the moment the resistance of the fluid becomes equal to the "active" force of gravity (in case of such small particles as we are dealing with here, this happens practically at the commencement of the falling movement).

We therefore find:

$$\frac{4}{3} \pi r^3 (S - S_1) g = 6 \pi r v \mu \text{ or } v = \frac{2}{9} g \frac{S - S_1}{\mu} r^2.$$

The velocity is thus proportional to the difference between the specific gravity of the sphere and that of the fluid, inversely proportional to the viscosity of the fluid and directly proportional to the square of the radius of the sphere. Should the suspended particle be of non-spherical shape, this formula will naturally give only an approximate idea of the influence of the size of the particle on the sinking velocity.

For Stokes' law to apply, the falling movement of the particle must take place in a fluid of infinite extension. In a suspension this is not the case. The falling particles will meet the upward currents produced by the sedimentation of the immediately preceding particles. The falling movement of the particles will consequently be hindered and this check will become more marked, the greater the concentration of the suspension. Theoretically this problem has been treated by Cunningham (13) and Smoluchowski (56). The first named has proved that in respect to more concentrated suspensions, Stokes' law must be modified by the introduction of coefficients, varying according to the different degree of concentration.

In trying to find out to what extent the hydrodynamic laws, as stated above, are able to explain the exceedingly great variations occurring in the sinking velocity of the red corpuscles, we find that varying differences between the specific gravity of the red corpuscles and that of the blood plasma are without demonstrable effect. Nor does the viscosity of the

plasma have any direct bearing on it. We even find here the fact, *a priori* unexpected and to be explained later, that the sinking velocity is as a rule higher in plasma of great viscosity.

Another factor, on the contrary, to which must be ascribed a fairly great influence is the degree of concentration of the suspension; in other words, the relative number of the corpuscles. If, in a sample of blood, containing, for instance, five million red corpuscles per cubic millimeter and the sinking velocity of which is twenty millimeters per hour, the number of red corpuscles be reduced by dilution with plasma to four million, the sinking velocity becomes increased nearly twice. A comparative investigation between the number of corpuscles and the sinking velocity, carried out on a great number of clinical cases, shows, however, the concentration of the corpuscles to be apparently of less importance than a dilution experiment of that nature would lead one reasonably to expect (Westergren, 2). There is certainly a factor counteracting the rapid sinking in anemic conditions, which probably stands in connection with the fact that the red corpuscles have relatively less tendency to aggregate in blood sparse in these elements. The red cell concentration becomes of decisive importance for the rapidity of sedimentation only in cases of marked polycythemia, where very low figures are obtained, or in marked oligocythemia, which in itself may occasion a considerably increased sinking velocity.

The factor, not yet mentioned, which has incomparably the greatest effect on the sinking velocity, is the radius of the particle. What an exceedingly great bearing this has for the falling velocity of suspended particles is borne out by experience in daily life. Large drops of rain fall rapidly to the ground, while the small drops of water in fog remain hovering in the air. Clay particles suspended in water form a stable suspension, while aggregations of clay, on the other hand, rapidly sink to the bottom. The red corpuscles may, it is true, vary somewhat in size in different cases; there is no doubt, however, that this difference in size has no appreciable influence on the variations in the sinking velocity. On the other hand, we find another property of the erythrocytes which is subject to very considerable variations and which vastly affects the radius of the suspended particles, namely, their tendency to form aggregations. It is this varying degree of aggregation which, as a quite predominant factor, determines the sinking velocity.

The microscopical study of a fresh blood drop taken from a healthy person shows that the red corpuscles are to a certain degree aggregated. This aggregation presents a characteristic architecture because the

corpuscles unite with their flat sides against each other forming what has been called piles of coins or rouleaux (Geldrollen). But the rouleaux in healthy blood usually do not contain very many corpuscles; they are somewhat irregular in form, do not show any great tendency to join together and consequently appear quite evenly distributed. (See fig. 1, left.)

A similar observation of blood from a severely diseased person or a pregnant woman gives quite another appearance. The rouleaux formation is so to say carried through with an incomparably greater energy. Each rouleau contains on an average very many more corpuscles and these are more closely and regularly united with each other. The great-

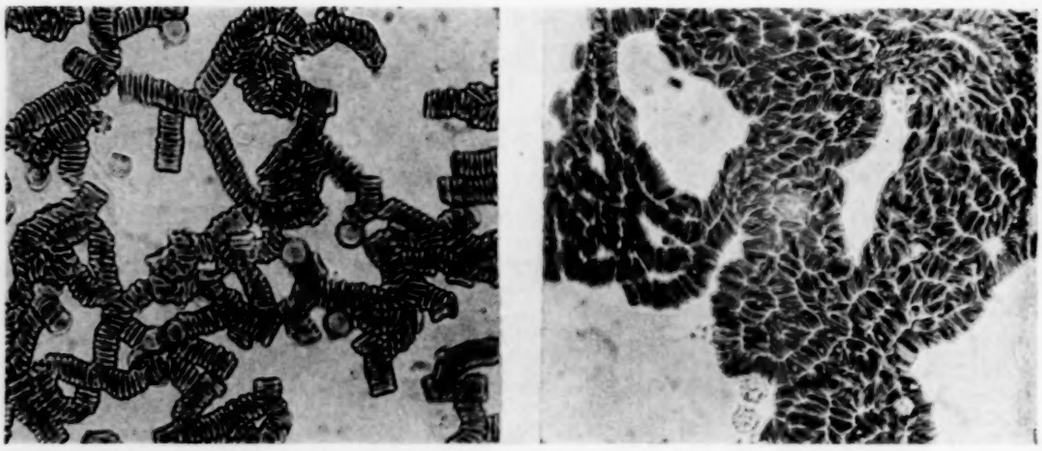

Fig. 1. Healthy blood, stability reaction 3 mm. and blood in pneumonia, stability reaction 93.

est difference between normal and pathological blood is, however, that the rouleaux themselves are clustered to a very high degree. The clusters are separated by large lakes of free plasma. (See fig. 1, right.)

This difference in the microscopic appearance of such specimens shows still more distinctly, if by means of pressure on the cover glass fluid currents are produced in the preparations. In normal blood the rouleaux fall apart at the slightest movement in the fluid, whilst the aggregates in pathological blood are not disturbed until very violent currents are produced. The rouleaux are strained and stretched like rubber tubes before they break. It is almost impossible though pressure on the cover glass to obtain a complete disaggregation. The aggregates are consequently not only larger in pathological blood, but have besides a decidedly more solid structure. Another characteristic difference is

that the formation of new rouleaux after disaggregation proceeds very much faster in pathological than in normal blood.

As far as has been observed, complete parallelism exists between the tendency to rouleaux formation and sinking velocity. The individual red blood-corpuscle may be considered as the primary particle which through aggregation with other red corpuscles gives rise to secondary particles of varying size. Assuming that the erythrocytes are spheres and that the aggregates formed by them are of spherical shape with the same specific gravity as the erythrocytes themselves (which is improbable since the aggregates must include some plasma), the sinking velocities (v and v_1) would be in a direct ratio to the squares of the radius of primary and secondary particles respectively. These radii being in the direct ratio to the cube roots of the volumes of the primary and secondary particles respectively we get $\frac{v_1}{v} = (\sqrt[3]{p})^2$, in which p denotes the number of primary particles, which the secondary aggregates contain. Accordingly an hundred-fold increase of the sinking velocity would correspond to a thousand-fold increase in the number of red corpuscles in the secondary aggregates. Such a computation is, of course, only exceedingly approximate but it helps to convey some idea of the association between aggregation and sinking velocity.

THE CAUSES OF THE INCREASED ROULEAUX FORMATION (1, pp. 114–144). As is evident from the foregoing, the increased aggregation of the erythrocytes seems to be only an exaggeration of a physiological phenomenon. There is no reason to presume any fundamental difference in principle between rouleaux formation in health and disease. The first question which arises is then whether the increased aggregation tendency of the erythrocytes is due to changes of the cells themselves, or to changes of the plasma.

Naturally the increased aggregation is in the end determined by a change in the surface layer of the red corpuscles, but as in other suspensions the properties of the surface layer of the particles and consequently the stability of the suspension, is mainly dependent upon the properties of the fluid medium. It would a priori appear probable that properties of the plasma are the determining factors in the suspension stability of the blood. Experiments in which washed normal corpuscles have been suspended in pathological plasma and vice versa and the sinking velocity measured have also shown that rapid sedimentation and strong aggregation are phenomena in a very high degree bound to the properties of the plasma.

That this is the case seems also probable from the results of experiments in which red corpuscles are suspended in plasma which has been diluted by addition of water or concentrated by evaporation. A 10 per cent concentration of the plasma, for instance, increased the sinking velocity from 56 mm. in thirty minutes to 104 mm., while a dilution to the same degree diminished the sinking velocity to only 20 mm. It seems then to be evident that the plasma contains substances which are the vehicle of its aggregation capacity—substances presumed to increase in pregnancy and disease. As it further proved to be the case that the red corpuscles do not aggregate and consequently settle extremely slowly when suspended in solutions which only contain the electrolytes of the plasma, and as, on the other hand, it could be shown that addition of many hydrophil colloids such as gelatine, agar, acacia, gummi arabicum, sodium salt of casein and nucleic acid, etc., strongly increase the aggregation, it seemed probable that the rouleaux formation in normal as well as pathological blood is caused by the hydrophil colloids of the plasma, the proteins, and that the degree of aggregation depends upon these proteins being altered in amount or properties during pregnancy and disease.

It has been known for many years that the quantity of the protein bodies mentioned is subject to considerable variations, in so far that the serum globulin or the fibrinogen, or generally both these protein fractions of the plasma, increase in amount during pregnancy and most diseases. Levinski, Landsberg and Krösing found the fibrinogen percentage augmented in pregnant women. The same fact in infectious diseases has been proved by Halliburton, Lackschewitz, Pfeiffer, Berggrün, Krösing, Dochez and many others during the last years. As to the degree of the fibrinogen increase it is generally very considerable and rises often to several hundred and even 1000 per cent of the normal values.

Equally rich is the literature on the increased amount of serum globulin in disease (Hoffman, Halliburton, Noguchi, Epstein, Rohrer, Adler and others). Generally the increase of serum globulin is accompanied by a corresponding decrease of serum albumin; in other words, the amount of serum protein is constant but the salt precipitation limit is displaced to the albumin side. This displacement may be so extreme that the globulin fraction—as in pneumonia—represents 95 per cent of the whole serum protein.

Attention may further be called to the fact that the lowest globulin values are to be found in the newborn, and that men seem to have a somewhat lower globulin percentage than women. (See Naegeli, 41.)

As will be seen, there exists a very marked parallelism between changes in the composition of the plasma protein, in the sense that increased sinking velocity of the red corpuscles and increased percentage of serum globulin and fibrinogen occur coincidently. The following experiments show that these two phenomena stand in direct causality.

In solutions of the different protein fractions of the plasma, prepared by precipitation with salts (ammonium and magnesium sulphate), the red corpuscles behave in a very different way. When suspended in a pure fibrinogen solution the erythrocytes show a very marked tendency to aggregate and settle with extreme rapidity. When suspended in a pure serum globulin solution, aggregation and fast sinking are not so pronounced, but still very marked. When suspended in a pure solution of serum albumin, on the other hand, the red corpuscles form a suspension of maximum stability, i.e., no aggregation occurs and the sinking is very slow. I will only mention one experiment performed with horse blood. In 5 per cent solutions of the different proteins the serum albumin suspension of erythrocytes gave a sinking value of 1 mm. after one hour, the serum globulin suspension one of 50 mm. in the same time, while corpuscles in the fibrinogen solution sank 110 mm. in ten minutes.

The property of the fibrinogen of furthering aggregation and sinking velocity, seems to be clearly evidenced also by the fact that the red corpuscles in defibrinated blood aggregate very much less and sink very much slower than in non-defibrinated blood—an observation made by Hewson 150 years ago. As example may be mentioned that two stability reactions of the same horse blood, made with citrated blood and with defibrinated blood, gave the figures 65 and 8 respectively.

To support my opinion that the increased sinking velocity in pregnancy and disease is caused by the above-mentioned plasma changes, I have determined the composition of the plasma protein and the stability reaction in the same clinical cases. This investigation proved that there exists a pronounced parallelism between the amount of fibrinogen or serum globulin and sinking velocity, a result which has been confirmed by many later investigators. (Linzenmeier, 35; Starlinger, 58; Frisch and Starlinger, 15; Gram, 18; Ley, 32; Noltze, 44; W. and H. Löhr, 37; Vorschütz, 62; Rosenberg and Adelsberg, 49; Petschacher, 46; Seki, 54; Holsweissig, 25; Bruchsaler, 11; Cooper, 12; Murakami and Yamaguchi, 39; Hille, 24, and others.)

As Starling (57) emphasizes, the different protein substances of the plasma may probably be regarded as forming a complex unit in the

living blood. From this point of view the increase of fibrinogen and serum globulin may be considered as a change of the general physical character of the protein of the plasma. As is well known, the fibrinogen is easiest precipitated by salts and forms a highly viscous solution. Serum globulin is not so easily precipitated by salts and its solution is less viscous, while serum albumin is the least precipitable and its solution has the least viscosity of the three. These facts probably explain the paradox already referred to, namely, that the sinking velocity is as a rule greatest when the viscosity of the plasma is high. The change in the general physical character of the plasma here in question may thus be considered as an augmentation of its globulin characters, or as a qualitative globulin increase.

In favour of this view we have furthermore the fact that heating blood serum to temperatures above 48°C. powerfully augments its aggregation capacity. This accords perfectly with the theory inasmuch as heating serum to these high temperatures augments the globulin fraction at the expense of the albumin fraction and further augments the euglobulin fraction at the expense of the pseudo-globulin fraction (Moll, Banzhaf and Gibson)—a circumstance of great importance in the preparation and concentration of antisera.

Another observation—still not theoretically elucidated, but which will probably be of great biological interest—is the fact that temperatures, corresponding to normal body temperature and its environment (30° to 48°C.), have a contrary, i.e., a strongly reductive effect on the aggregation power of serum and plasma. A peculiar, and as yet unexplained, phenomenon in this connection is that if the test-tube be shaken during such heating the decrease in the aggregation power of the serum or plasma does not occur (see 1, p. 189–228).

It is hardly necessary to point out the fundamental difference in principle between serological hemagglutination and the rouleaux formation of erythrocytes. In the former case we are dealing with specific substances present only in small quantity but intensively active, the so-called agglutinins; in the latter case with non-specific substances active only in comparatively great concentration through their general physical character.

It must, however, be recognized that other factors probably exist which may influence such a sensitive mechanism as that of rouleaux formation. The lipoids of the plasma, as well as the proteins of the stroma of the erythrocytes, have been considered to be of importance (see 2 and 3) but it seems to me that these factors, at least when we

are chiefly concerned to explain the variable suspension stability of man, certainly are of very much less significance than the globulin increase.

Finally, it should be added that the gases of the blood have a not unimportant influence upon the sinking velocity. Experiments in vitro by Leendertz (31) have shown that the sinking velocity is increased if oxygen is bubbled through citrated blood. Carbon dioxide, on the contrary, decreases the sinking velocity. These facts probably explain why the stability reaction in cyanotic conditions as a rule gives comparatively low values.

THE ROULEAUX FORMATION AS PHYSICO CHEMICAL PHENOMENON (1, pp. 145–155). As is well known, the stability of suspensions to a great extent depends upon the physical characters of the interface between the particles and the fluid.

Every surface of contact of one substance with another substance of less molecular force tends to diminish on account of the so-called surface tension. Two particles in a suspension coming close enough to each other, the interfaces between each one of them and the fluid will join to one continuous interface. This, tending to diminish, will press the particles together.

There is hardly another model existing so beautifully demonstrating the action of the surface tension as the rouleaux formation in the blood. When two previously solitary corpuscles in a fresh drop of blood, microscopically studied, come into contact with their broadsides, we get the impression that they are pressed together by invisible forces. If the first point of contact is situated at the edge of the one or both corpuscles, which also very often happens, the corpuscles instantly perform a quick motion, the one gliding up against the other, broadside against broadside. The motion does not stop until the peripheral edges of the corpuscles are brought to a position corresponding to the surface of a cylinder. The rouleaux formation is thus a mechanism manifestly proving the existence of a force which tends to diminish the interface between corpuscles and plasma to a minimum. If stickiness, which has played a great rôle in theories of agglutination, gave rise to the aggregation here in question, the corpuscles would remain in the position of their first contact and we should not obtain the peculiar architecture of the aggregates, the rouleaux formation.

But there are also other forces which must be taken into consideration with regard to the degree of aggregation tendency of the red corpsucles. The interface between the particles and the fluid of a suspension is

probably always the seat of electric forces. On each side of the interface there exist electric charges, which are of different signs and of equal magnitude, thus balancing each other. The existence of an electric double layer is most easily proved by the fact that the particles migrate when an electric current is passed through the suspension. The fact that the red corpuscles in their native medium, the plasma, migrate towards the anode is a proof of the fact that they are charged with negative electricity.

While the surface tension represents the attraction force between the particles of a suspension, the existence of an electric charge acts as a repulsive force between them. This effect is brought about in two ways, partly directly on account of the fact that bodies charged with the same kind of electricity mutually repel each other, and partly indirectly on account of the fact that the electric charge of a surface tends to increase it, consequently acting in opposition to the surface tension. The last named point of the effect is easily understood, if we consider that the elements of the surface, being charged with the same kind of electricity, must tend to repel each other.

There is, however, a third circumstance which is of influence upon the stability of suspensions. There are several facts which lead to the supposition that the particles of a hydrosol are surrounded with a layer of adsorbed water, which prevents the aggregation of the particles or makes it more difficult. Principally, on account of the great difference in viscosity of different colloids, this water binding capacity of their particles is considered to be of a very different degree. The hydration is not very pronounced in the typical suspensoids, which have almost the same viscosity as their fluid medium, whilst one of the most characteristic properties of the emulsoids, namely, their great viscosity, is a proof of the great capacity of their particles for binding water. The difference in this respect is considered to be the chief cause of the instability of the first-named class of colloids, and of the comparatively great stability of the last-named ones.

That the degree of hydration of the red corpuscle surfaces is of importance for the degree of their aggregation tendency, we must conclude from the fact that the surface layer of the erythrocytes consists of emulsoids. Another circumstance, which probably speaks in favour of regarding the red corpuscles as surrounded with an adsorbed water layer, is, that the relatively high viscosity of the blood is dependent upon the erythrocytes to a very high degree.

As the influence of the electric charge exerts an effect upon the surface

tension, so there exists also, in all probability, a causality between electric charge and hydration of the particles. It has been shown that electrolytes which reduce the charge of the particles in a colloidal silver solution also reduce its viscosity. Zsigmondy (64) and Pauli (45) regard the fact that protein solutions, in which the particles are charged, are more viscous than solutions in which they are not charged, as depending upon the charged particles being more hydrated.

Considering these factors which influence the stability of suspensions it is not surprising that the mechanisms having to do with the stability of the blood must be regarded as very complicated and far from clear. As stated above the problem seems to hinge upon the manner in which the globulin increase changes the interface between the red corpuscles and the plasma or, let us say, the surface of the red cells. Is it by increasing the surface tension, or by reducing the negative electric charge of the corpuscles or finally by depriving their surface colloids of adsorbed water? The author (16) and after him Linzenmeier (35), have made experiments in Höber's laboratory discharging the corpuscles with positive ions in different concentrations—experiments tending to show that the globulins decrease the negative charge of the corpuscles. But, on the other hand, the pronounced parallelism between the magnitude of the aggregation effect of the globulins and other emulsoids upon the erythrocytes and their degree of viscosity speaks in favour of the theory that a dehydration of the corpuscle surface layer may be the predominant factor. See also Heidenhain (21), Wiltshire (61).

THE ERYTHROCYTE AGGREGATION IN THE STREAMING BLOOD (1, pp. 157–167). The rouleaux formation is not exclusively an extravascular phenomenon, as for instance is the coagulation of the bood which is caused only by conditions not present within the vascular system under normal conditions.

The tendency of the erythrocytes to aggregate within the vessels can be established by estimating the sinking velocity of these cells in vivo. The experiment is most conveniently carried out with two tourniquets three to five inches apart on the forearm sufficient to stop the circulation in the superficial veins. The forearm having been kept in a vertical position for some time, say 15 minutes, blood is collected by puncture from an easily visible vein immediately below the uppermost of the two constrictions. Blood specimens thus obtained will be different in persons with different suspension stabilities. In a healthy man they appear made up of whole blood, indicating that the red corpuscles have not settled to any appreciable extent. In pregnant women or diseased

individuals, on the other hand, not blood but plasma, more or less devoid of red corpuscles, is obtained, the red cells having sedimentated in the vein during the experiment, the cause being of course the same as in the experiments in vitro, i.e., augmented aggregation of the erythrocytes.

It is likewise possible to verify, by direct observation, the formation of aggregates within the vascular system. This can be done, as was shown by Ploman (47), by ophthalmoscopic observation of the retinal vessels, the blood pressure in the central retinal artery at the same time being counterbalanced by pressing a finger on the eye-ball. In normal persons a number of seconds must elapse after the arterial flow is stopped before a fine granulation can be seen in the vascular beds. In patients with a high sinking velocity, the picture becomes changed almost at the same moment as the ocular pressure is increased and this, furthermore, to an incomparatively very much greater extent. The red continuous streaks are almost immediately transformed into great clumps evidently consisting of aggregated erythrocytes, which mark the situation of the vessels like strings of red beads. On varying the intraocular pressure with the finger on the globe, the blood moves about in different directions in the vessels, and an interesting feature is then noticed, namely, that the aggregations endure even in rapidly streaming blood. There are even rare cases in which a granulated blood stream may be seen in the retinal vessels without artificially decreased stream velocity, as for instance in pneumonia.

The different degrees of intravascular erythrocyte aggregation, however, can be directly observed also in another way, namely, by microscopy of the skin capillaries, most conveniently done with the capillaries at the base of the finger nail. In a normal person careful focussing is required to convince the observer that the blood is flowing at all, because of the even distribution in the blood-current of the erythrocytes, which separately are scarcely or not at all visible. As is well known the rapidity of the stream varies in different capillaries and in the same capillary from time to time. When the stream is for the moment slow, it is possible to recognize a certain degree of granulation. This of course corresponds to the fact that even in a fresh specimen of normal blood, studied in vitro, some rouleaux formation occurs. The same examination carried out on a pregnant woman or a patient with increased sinking velocity, gives an entirely different picture. Here the red corpuscles are joined into elongated, more or less connected clumps, which run along in almost all capillaries, finding their way like eels through the vessels. Altogether there exists between the extent of this so-called granular

current in the cutaneous capillaries and the degree of sinking velocity, as tested in vitro in the same person, a pronounced parallelism. My observations and my opinion of the nature of this phenomenon have been confirmed by some authors (Linzenmeier, 34); (Neergard, 43), and denied by others (Kürten and Gabriel, 30). The last named consider that "körnige Strömung" in the skin capillaries is only a consequence of slowness of the stream and thus of a locally disturbed circulation. They found cases with extremely high sinking velocity without seeing a granulated blood stream. This may be right, but the explanation is that a maximum of instability of the blood does not give rise to many small aggregates, but to *one* great aggregate which occupies the centre of the vessel in its total length.

Microscopical observations of the circulation in horses prove the correctness of this interpretation. As already mentioned, the horse has an enormously strong rouleaux formation and an extremely great sinking velocity even under normal conditions. The study of the blood stream in the fine vessels of the mesentery of the living horse does not give at first sight the impression of a granulated stream. But closer observation makes it clear that this is due to the fact that the corpuscles are so strongly aggregated that they do not separate. The blood of the horse in the finer vessels is really not at all a suspension, the erythrocytes running along as a compact coherent string in the middle of the vessel; only when the stream is slowed by pressure on the supplying arteries does the string show granulated outlines and finally break to pieces.

A pathologic—anatomical consequence of the intravascular aggregation of the erythrocytes may here be shortly mentioned, namely, the occurrence of well developed fibrin coagula in the dead body. The nature of this phenomenon, quite clear to older physicians, has been vividly discussed by leading pathologists of modern times. Ribbert (48) thought them to be the consequence of an "agonal thrombosis" in the yet streaming blood; Marchand (38) considered that they owed their origin to delayed coagulation. Aschoff (5) finally also reckoned with the possibility that the red corpuscles may settle more rapidly post mortem in some bodies than in others. Having had the opportunity during some years of making autopsies on persons in whom the suspension stability was measured shortly before death, I may emphasize that strongly developed fibrin coagula are found only in cases which had previously a great sinking velocity. The finding of cruor coagula without a fibrin layer, on the contrary, is typical for cases where the sinking velocity is normal. Inequalities of the coagulation time of the

blood in the dead body may naturally be of influence upon the appearance of the post-mortem clots. The degree of rouleaux formation and the sinking velocity of the erythrocytes are however, as a rule, of far greater importance. (See further 1, pp. 182–188.)

THE FLOW OF SUSPENSIONS THROUGH NARROW TUBES (17). At first a few words must be said about the hydrodynamic laws which apply to the flow of suspensions through tubes of fine calibre. This is a part of hemodynamics where our knowledge hitherto has been incomplete or erroneous and which has an important bearing also on other hematological questions of great moment.

In the case of a fluid flowing through a tube, we know well that the speed of the current is greatest in the centre, gradually diminishing toward its wall. A reverse condition prevails as regards the pressure within different parts of the fluid, that is to say, it is least in the centre of the tube, from where it gradually increases toward the wall. A particle situated in the moving fluid somewhere between the axis and the wall of the tube will be exposed to a greater pressure on the side facing the wall, than on the side facing the axis. Therefore the particle will be subjected to a force striving to carry it in a direction toward the axis. Obviously this force will increase with the distance between the peripheral and axial side of the particle, a bigger particle consequently being more liable than a smaller one to be moved away from the wall and toward the centre of the tube.

A fluid containing a considerable quantity of suspended particles will, therefore, be divided, the particles moving along the axis of the tube, i.e., in the so-called axial current, while the fluid will be more or less completely relegated to the wall of the tube, constituting the so-called peripheral current. If the fluid contains particles of different sizes, the bigger ones will tend to occupy the central part of the current to a higher degree than the smaller ones and should the bigger particles take up a comparatively great portion of the volume of the suspension, the smaller particles will in consequence be more or less completely confined to the peripheral current.

Since the speed of the current increases with the distance from the wall of the tube, the particles will attain a greater average speed than the fluid, and among particles of different sizes those of larger size will move along quicker than the smaller ones. This difference in speed of the different constituents of a suspension is of great consequence for understanding the distribution of the blood-cells within different areas of the vascular system.

To render this more clear, let us assume a suspension in a receptacle A from which it flows through a capillary tube to a receptacle B. Let us further assume that the volume of the particles and the volume of the fluid are in the proportion of 1:3. As the suspension flows through the tube, the particles will move along more rapidly than the fluid. For the sake of simplicity, let us again assume the average speed of the particles to be twice that of the molecules of the fluid. The consequence is that during the transit of the suspension through the tube, the particles will only stay within the tube half as long, on an average, as the fluid parts; this naturally means that the relation of the volume of the particles to that of the fluid in the flowing part of the suspension within the tube will be in a ratio of 1:6.

On the other hand, should the relation between the average speed of the particles and that of the fluid be unknown, it can be estimated by determining the volumetric relationship between the particles and the fluid in the original suspension, and also the analogous relationship in the suspension flowing through the tube. If, in using the same figures as in the previous example, the former ratio has been determined to 1:3, and the latter has been found to be 1:6 the first of these fractions divided by the second will give the average speed of the particles to that of the fluid parts, i.e., 2:1.

In the case of a suspension with particles of different kinds, the relation between their average speeds can be determined in an analogous manner, that is to say, by estimating the relative number of particles of different kinds in the original suspension, as well as in that part of it flowing through the tube. Having thus found out the relation between the average speeds of the different particles, one is then in a position to form an opinion as to the relative situation of the particles in the cross section of the tube during the flow of the suspension. Evidently the more rapid particles have moved along lines in the current situated at a shorter distance from the axis of the tube than is the case with the more slowly-moving particles.

THE BLOOD IN THE VASCULAR SYSTEM AS A STREAMING SUSPENSION (17). Blood is drawn into a glass capillary tube. The completely filled tube is centrifugalized. This gives the approximate relationship of corpuscles to plasma. The relationship between red and white cells may be obtained, if desired, by making blood counts of the contents of the filled capillary, the capacity of which is known. We thus have the composition of the blood. Similar determinations are now made on the contents of the same or an identical capillary tube

through which the blood has been made to *stream*. For the sake of explicitness only, it may be mentioned that the first drops passing the capillary hold relatively more of the fastest flowing constituents of the blood—just as much more as these constituents are lacking in the the blood streaming within the tube. The diameters of the glass capillaries employed have varied between 1.5 and 0.05 mm. In principle the length of the tube is insignificant for the result. It is only a question of obtaining suitable quantities for the blood count and advisable length of the tubes for centrifugalization.

Table 1 gives the change in the volumetric relationship between the erythrocytes and the plasma, when blood from a healthy person is streaming through glass capillaries of different diameter, and likewise the calculated average velocities of the erythrocytes in proportion to

TABLE 1

DIAMETER OF THE TUBES	VOLUME OF THE BLOOD		AVERAGE VELOCITY OF THE ERYTHROCYTES; THAT OF THE PLASMA = 100
	Erythrocytes	Plasma	
mm.	*per cent*	*per cent*	
1,100	40.5	59.5	100
0,750	40.1	59.9	101
0,450	39.8	60.2	103
0,250	39.2	60.8	106
0,095	33.6	66.4	135
0,050	28.0	72.0	175

those of the plasma. These figures show that with decreasing diameter of the tubes below 0.1 mm. the relative erythrocyte volume is very rapidly decreasing, the velocity of the erythrocytes on the other hand in proportion to that of the plasma very rapidly increasing.

A biologically important consequence of the blood becoming poorer in red cells during the passage through narrow tubes and at the same time a further proof of the fact itself, is the behaviour of the relative viscosity of the blood in glass capillaries. This property has not been systematically investigated in very narrow tubes, which explains the doctrine (22) generally embraced that, on the whole, the blood follows the law of Poiseuille; in other words, behaves like a fluid with regard to its viscosity. Unpublished investigations by the author have shown, however, this not to be the case. The relative viscosity of the blood is found highly reduced in capillaries of a diameter below 0.1 mm., the reduction being perceivable even in tubes of about 0.3 mm. in diameter. As

an example may be mentioned the fact that the relative viscosity of normal blood is 30 per cent lower in a capillary 0.05 mm. in diameter than in one 1 mm. in diameter. The explanation of these experimental results is undoubtedly the fact that blood, streaming in narrow tubes, is relatively much richer in plasma and poorer in corpuscles than it is when streaming in larger tubes.

There would not seem to be much doubt that the same changes—dilution of the corpuscle suspension and decrease of the viscosity of the blood—also occur in the body as the blood flows through vessels of corresponding diameters. The layer of fluid next to the glass- or vessel wall is stationary, while the flowing portion of the contents in both cases is moving, strictly speaking, within a plasma tube.

Regarding the different distribution of the red cells within the vascular system, an analogous opinion, founded upon experiments of quite another nature, has earlier been suggested.

Whipple and his co-workers (55) some years ago pointed out, that the large discrepancy existing betweeen the values obtained for the circulating blood volume by different methods must depend upon the erroneous supposition that the blood has the same composition in all parts of the vascular system. A comparison between values obtained with the monoxide method, by which only the red cell volume is directly determined, and the dye method, by which only the plasma volume is directly determined, has led the above mentioned authors to the conclusion that a very considerable amount of the total blood volume, namely, that portion which is contained in the small vessels must be relatively richer in plasma than that portion which is contained in the heart and in the larger vessels.

That this different distribution of the blood cells generally has been overlooked depends, *inter alia*, upon the fact that a drop of blood from the finger or the ear shows—at least regarding the red cells—the same composition as blood from an artery or a vein (41). But the composition of a drop from bleeding narrow vessels is not the same as the composition of the blood in the vessels themselves. It must be kept in mind that the red cells, forming the axial current, enter the drop with greater velocity than the plasma and thus accumulate in the drop. The fact that the drop gets the same composition as the blood in the larger vessels proves therefore really that the blood in the narrower vessels is poorer in corpuscles.

Regarding the position of the leucocytes in the blood stream in small vessels the universally accepted opinion, based on Schklarewsky's (51)

observations, is that these cells stream in the peripheral layer of the bed —the reason of this being, as maintained by all hand- and textbooks, that the specific gravity of the white cells is lower than that of the red ones. In the frog, generally used in such studies, the white cells do predominate in the peripheral zone but in mammals the opposite is the case as has been demonstrated by experiments with capillary tubes, as described above. Here the evidence clearly shows that the leucocytes occupy the axial zone. The relative difference in size of the white and red cells in frog and mammalian blood gives the key to the true explanation of the phenomenon. In the frog the huge red cells claim the axial, fast-moving zone and thrust the small white cells into the peripheral stream; in mammalian blood in which the factor of size is reversed the leucocytes predominate in the axial zone. Differences in specific gravity of the cells have no influence upon their position in the stream.

A very easy way of showing that in normal human blood the leucocytes indeed move more rapidly in the stream than the red cells is to suck up a drop of blood in a glass capillary. When the drop has been moved a certain distance the white corpuscles are closely collected behind the leading meniscus—the biggest white cells, namely, the mononuclear and the polynuclear leucocytes, being placed ahead of the lymphocytes.

Quantitative treatment of the problem in the above mentioned manner gives the following result. A blood specimen with 9,600 white corpuscles per cubic millimeter has this number reduced to 5,800, when streaming through a glass tube 0.27 mm. in diameter. The erythrocytes at the same time are decreased from 5 millions to 4.7 millions per cubic millimeter, so that the average speed of these cells to that of the white corpuscles must thus have been as 100 to 156.

As these figures show, the blood in the narrower must contain per cubic millimeter only a fractional part of the leucocytes present in the larger vessels, provided the suspension stability is normal—*notà bene*, with regard to the streaming leucocytes. How many of these cells are momentarily adherent to the walls of the small vessels at present evades computation.

THE BIOLOGICAL SIGNIFICANCE OF REDUCED SUSPENSION STABILITY (17). The suspension stability of blood is a term having the advantage of including *a*, the tendency of the erythrocytes to aggregate; *b*, the degree of aggregation itself, where it is able to take place—as in the small vessels during normal circulation and in the large ones when the currents

are diminished—and *c*, the increased sinking velocity in vitro, which is its most important consequence in ancient and modern clinical work.

Changes in the suspension stability can be conceived as of biological importance in a twofold manner. The tendency to aggregate more than normally naturally suggests, as indicated above, some change in the surface layer of the erythrocytes which might produce some change of their function. On this point, however, no investigations have been published, as far as I know. But the consequences of the increased aggregation itself in the flowing blood are easily understood, if the foregoing statements are accepted.

Aggregation of the red corpuscles may, as said before, be regarded as implying an artificial enlargement of the primary particle, the individual red corpuscle. A marked intravascular aggregation of the erythrocytes will therefore result in the following phenomena. The red corpuscles will now, more than before, be transported in the central parts of the current. Microscopical study of the appearance of the blood-stream in capillary glass tubes containing blood of different sinking velocities, will show a moving picture of the different current conditions. In blood of normal sinking velocity, that is to say, a couple of millimeter per hour, the red corpuscles are seen to move along in a suspension of uniform appearance in nearly the whole width of the current. It is only the most peripheral layers that are free from cell elements. In blood of high sinking velocity, for example, 100 mm. per hour, we find the red corpuscles clustered together into a more or less uniform snake-like formation, moving along in a narrower, sharply defined axial current, surrounded on all sides by a broader layer of plasma. In more pronounced cases the red corpuscles may completely occupy the central part of the current, while the plasma is entirely relegated to the wall layer. See figure 2.

Of still greater consequence, however, is the increased intravascular erythrocyte aggregation for the distribution of the white blood corpuscles within the vascular system. If, assuming that the red corpuscles reach such a considerable degree of aggregation as to exceed the white cells in size, and further, if taking into consideration that the red cells occupy a great portion of the volume of the blood, the only conclusion to draw is that the white cells, from having previously moved along in the centre of the vessel will now come to occupy the peripheral current and from having previously moved along more rapidly than the red corpuscles they will now be moved more slowly. The result is that the blood in the finer ves-

sels will be richer in white cells than before, whereas the blood in the bigger vessels will be correspondingly poorer in these cell elements. As an illustration the following instance may be cited: a sample of blood with a sinking velocity of 50 mm. per hour held 5,000,000 red cells and 8,300 white cells. During the flow through a capillary tube of a diameter of 0.27 mm. these figures became changed to 4,100,000 and 8,400 respectively. In this case, therefore, the white blood corpuscles had moved with a velocity of about 20 per cent *less* than the red cells. How the white corpuscles behave in blood of reduced suspension stability streaming through a glass capillary is clearly shown by figure 2.

The suspension stability of blood may be promptly reduced, i.e., altered in a direction of increasing the aggregation tendency of the erythro-

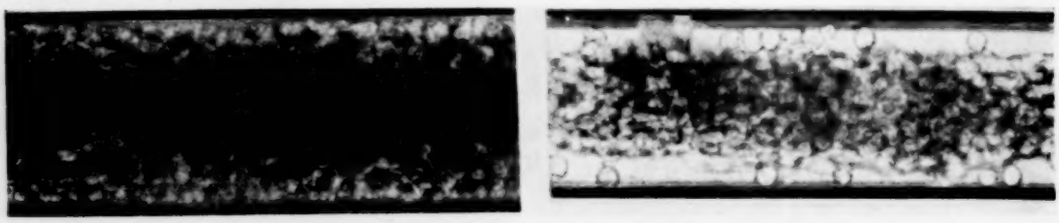

Fig. 2. Healthy blood, stability reaction 3 mm. and blood in pneumonia, stability reaction 93 mm. Drawn up in glass capillaries and photographed at the instant motion ceased. In the preparation of the last named blood all the marginally located cells are leucocytes.

cytes in vivo, by intravenous injections of certain hydrophil colloids, as for instance gelatine. If, while the mesentery is kept under microscopical observation, a guinea pig be injected with a few cubic centimeters of a 10 per cent gelatine solution the contents of the narrow vessels almost immediately exhibit a strikingly changed appearance. Before injection the axial current of the red corpuscles gives only a diffuse picture of a streaming motion, the suspension stability of the guinea pig being high. The peripheral current is seen to contain plasma and some white corpuscles which, however, do not move along with the current but are fixed to the wall of the vessel—a phenomenon due to the fact that the leucocytes, in contrast to the erythrocytes, apparently possess the property to agglutinate with the endothelial cells of the vessel wall. The white cells adhere when the blood-stream, as occasionally occurs, becomes very slow or stops, the hydrodynamic forces regulating the flow of the different constituents of the blood then being suspended. The gelatine having been injected, the first change occurs in the axial

current which takes on the appearance of a granulated stream, described above. The next moment the peripheral current also changes in aspect; the white corpuscles collect in great quantities and adhere in great numbers to the vessel walls. This increase in the number of the leucocytes in the peripheral vessels must naturally correspond to an equally prompt decrease in the central vessels, a blood count from a larger vein made at this time showing indeed that the relative number of the white cells is markedly reduced, generally more than 50 per cent. In a rabbit, for instance, injected with 10 cc. gelatine solution, the number of leucocytes fell in a few minutes from 15,000 to 4,000 cubic millimeters. It is possible that the clean cut results of these experiments depend not alone upon an increased aggregation tendency of the erythrocytes, but also upon a similar increased aggregation tendency between the leucocytes and the endothelial cells of the wall of the vessel.

In this connection it ought perhaps to be mentioned that the red and white corpuscles never show any tendency to aggregate with each other. Whether there are conditions in which the white cells cluster between themselves in the streaming blood, as is often seen in vitro (Schilling and Schulz, 50), is not known. If there are such conditions yet another factor must be taken into consideration with regard to the complicated behavior of the cells in the vascular system.

In summing up, it may be said that the capacity of the organism to vary the degree of intravascular erythrocyte aggregation constitutes a mechanism which changes the arrangement of the different constituents of the blood in the cross section of the narrow vessels, as a consequence of which their relative velocity of circulation is altered in this part of the vascular system—a result which, of necessity, alters the composition of the blood in the narrow vessels and in the larger ones as well.

What this means from a general biological point of view is yet, in many respects, difficult to conceive. But with regard to the changed distribution of the white corpuscles within the vascular system, the causality seems to be more clear.

One of the most significant occurrences in the whole process of inflammation, is the out-wandering of leucocytes through the walls of the small vessels. The first step in this process is necessarily the adherence of the white cells against the vessel walls. It seems probable to me that the globulin increase of the plasma in infectious diseases is of great significance for this process, the white corpuscles being transferred in the above described manner to the frontiers. The teleological explanation of the reduced suspension stability in pregnancy may then probably be

considered as an increased readiness to meet injuries of such kinds, for the combat of which the white corpuscles play a rôle.

But the increased aggregation of the erythrocytes in the vascular system during pregnancy and in disease is probably of importance also for the task which these cells themselves have to fulfill. In my opinion one reason why the hemoglobin is enclosed in corpuscles is that this guarantees to the hemoglobin a relatively more rapid transport in that part of the vascular system where the circulation is slow, i.e., in the narrow vessels. But this advantage of the hemoglobin over the plasma will be more marked if the erythrocytes are aggregated, the aggregates, as stated above, reaching the functional destination of the red corpuscles, namely, the capillaries, more rapidly than the isolated units.

In this connection, it should be pointed out that quite peculiar circumstances of great physiological interest with regard to the function of the red corpuscles develop when the blood passes capillaries of active organs. The muscle capillaries are so narrow that a single corpuscle will completely fill the lumen of the vessel (Krogh, 29). Consequently no division in axial and peripheral current can occur. This being the case, the average velocity of the red corpuscles will naturally be diminished to that of the plasma. The blood will therefore in the true capillaries receive back the high hemoglobin percentage which it had in the larger vessels, but which in the next moment, on entering the peripheral veins, will again be lost.

For the best utilization of the hemoglobin-store of the organism it is essential that a maximum of this substance with a maximum of free surface be present in the capillaries; and it is further essential that the transport of this substance from the capillaries of the lungs to those of the tissues and vice versa should be as rapid as possible. These ideal conditions seem to be realized to a high degree in the horse, where the single corpuscles are very small but their aggregation tendency is exceedingly great, for the aggregation of the corpuscles in the narrow vessels not only guarantees a faster transport of the red corpuscles, but as a consequence leads to an increased concentration of these cells in the larger vessels and, as has been demonstrated, thus also in the true capillaries.

PATHOLOGICAL CONSEQUENCES OF REDUCED SUSPENSION STABILITY (1, p. 168). On the other hand, it is not unlikely that a highly increased aggregation tendency of the erythrocytes may sometimes constitute an element of danger, the suspension stability of the blood being so reduced that its fluidity is jeopardized.

Virchow once defined thrombus formation as an intravascular coagulation of the blood. Later work, however, has shown that this definition only applies to a minor group of thrombi, the larger and more important group being the so-called aggregative or pulsative thrombi. These are chiefly formed by an aggregation of the cell-elements and arise only in the flowing blood. There is no doubt that the thrombocytes play the leading rôle in their formation, but most writers agree that the erythrocytes may participate even in an early stage. It thus seems beyond doubt that, in the already complicated etiology of the thrombosis, consideration must also be given to the increased tendency of the red corpuscles to aggregate. And this opinion is strengthened by the fact that thrombosis of this type and increased sinking velocity occur coincidentally, the thrombi occurring chiefly in most infectious diseases, and especially in pneumonia, where the suspension stability is so markedly reduced, and furthermore, during pregnancy and the puerperium where thrombi of non-infectious origin not infrequently occur (Klein, 28). Another possibility worth investigating is that the globulin increase not only augments the aggregation tendency of the erythrocytes but also of the thrombocytes, which from our present standpoint would be of vital moment in the etiology of thrombosis. In this connection it may be pointed out that the eminent French hematologist, Hayem (20), long ago observed that the blood in inflammatory diseases, besides being rich in fibrinogen, is also characterized by an increased tendency of the thrombocytes to agglutinate.

There is still another kind of thrombosis in which the aggregation tendency of the erythrocytes must be considered to be of primary and quite predominant importance, namely, the thrombi solely consisting of red corpuscles and described as characteristic in the capillaries in certain morbid conditions. Schmorl's (52) classical researches showed that the pathological anatomy of eclampsia, the severest of the complications of pregnancy, is characterized by multiple capillary thromboses with accompanying necrotic changes, especially in the liver and the kidneys. These organs are described by Schmorl in the following way: "Schon bei der Untersuchung von dem frischen Organ entnommenen Schnitten findet man sehr häufig dass zahlreiche Kapillaren und kleine Venen so vollgestopft sind mit roten Blutkörperchen, dass dieselben unter Verschwinden ihrer Konturen zu einer homogenen, roten, glasigen Masse zusammengesintert sind, welche das Lumen der betreffenen Gefässe prall ausfüllt."

The organic changes which are constant and most typical for eclamp-

sia are located in the liver. The thrombi are predominant in the finest branches of the portal system. Those parts of the liver parenchyma in the neighborhood of the thrombi are necrobiotic. Schmorl regarded this picture as absolutely pathognomonic for eclampsia but, as Beneke (6) has pointed out, it has a striking equivalent in the liver change produced by the injection of hemagglutinating sera.

As there are reasons to believe that the aggregation tendency of the erythrocytes in eclampsia is greater than in normal pregnancy, because of the pronounced polycythemia existing in this disease (Zangemeister, 63)—relatively much stronger than the values of the stability reaction indicate—it seems probable that the intravascular aggregation of the erythrocytes in eclampsia may explain, at least to a high degree, the predominant characters of the anatomical changes found post mortem. Similar capillary thrombi are also often found in infectious diesases, as pneumonia, diphtheria and abdominal typhus. (See Beneke, 6.)

Intravascular aggregation of the erythrocytes may be of even greater pathological importance than has been thought because it is difficult to determine, in the microscopical preparations, whether the aggregates have been sufficient to produce embolism. Unpublished investigations by the author indicate that a considerable pressure is necessary to force the aggregates of erythrocytes in blood, the suspension stability of which is strongly reduced, through narrow glass capillaries—a pressure of 20 mm. Hg, for instance, being required to drive blood with a stability reaction of 100 mm. through a glass tube 0.1 mm. in diameter. In such a case microscopic inspection shows that the difficulty is due to the aggregates which plug the entrance of the tube. Normal blood, on the contrary, will flow through a similar capillary with very much lower pressures. It seems to me obvious from the results of these experiments that circulatory disturbance in the narrow parts of the vascular system as a consequence of falling blood pressure, for instance *sub finem vitae*, must be more marked in patients with strongly reduced than in patients with a more normal suspension stability of the blood.

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APPLICATION OF STATISTICAL METHODS IN PHYSIOLOGY[1]

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Paper from the Department of Biometry and Vital Statistics, School of Hygiene and Public Health, The Johns Hopkins University, Baltimore, Md., No. 150

Statistics have been collected in almost every field of scientific endeavor and they are reported in a very large proportion of physiological papers. A tabulation of quantitative and non-quantitative papers for every fifth year in the American Journal of Physiology illustrates the degree to which statistics are collected by physiologists.

YEAR	NON-QUANTITATIVE	QUANTITATIVE	PER CENT QUANTITATIVE
1898	22	14	39
1903	35	34	49
1908	70	26	27
1913	39	17	30
1918	61	56	48
1923	87	100	53
1927	120	167	58

The pertinent fact about these observations is that physiology has always been a subject which deals to a very high degree with quantity and frequency.

Statistical method represents the ways and means of handling quantitative data. It has been applied to statistics in almost every domain and in all instances has proved itself to be effective, consistent and indispensable. Since physiologists are dealing in a very large measure with quantitative material, they should seriously consider what statistical method has to offer them in the form of ready-made tools of analysis.

There are scores of definitions for statistical method. Those of Yule (687, p. 5) are all inclusive and consequently most commonly accepted.

> By *statistics* we mean quantitative data affected to a marked extent by a multiplicity of causes.

[1] The author expresses his appreciation to Dr. Lowell J. Reed for his criticism of this paper, and for some of the general thoughts expressed therein.

By *statistical methods* we mean methods specially adapted to the elucidation of quantitative data affected by a multiplicity of causes.

By *theory of statistics* we mean the exposition of statistical methods.

These definitions implicitly assume that the observations to which statistical methods are applied have been carefully taken. Clean-cut definitions of material and experimental technique are indispensable prerequisites. Statistical workers who fail to scrutinize the goodness of their observed data and carry through a satisfactory analysis upon poor observations, will end up with ridiculous conclusions which cannot be maintained.

Statistical reasoning centers about the probable error concept, and the adaptation of this concept to the study of variable data. Assumptions are made in the development of statistical inference equations; common sense aids by telling when to apply the equations to observed experience in light of the assumptions which have been made.

In order to gain some knowledge of the degree to which statistical logic is being used, a survey was made of a sample of 200 medical-physiological quantitative papers from current American periodicals. Here is the result:

a. In over 90 per cent statistical methods were necessary and not used.
b. In about 85 per cent considerable force could have been added to the argument if the probable error concept had been employed in one form or another.
c. In almost 40 per cent conclusions were made which could not have been proved without setting up some adequate statistical control.
d. About half of the papers should never have been published as they stood; either because the numbers of observations were insufficient to prove the conclusions or because more statistical analysis was essential.

Statistical methods must eventually become an essential tool for the physiologist. It will be the physiologist who uses this tool most effectively and not the statistician untrained in physiological methods.

The subject matter of physiology deals primarily with results of experimentation. Determinations of cause and effect are dominant themes.

The more perfect the experiment—(Yule, 689, p. 3)—the more nearly the experimental ideal is attained—the less is the influence of disturbing causes, and the less necessary the use of statistical methods. The more imperfect the experiment—the greater the failure to attain the experimental ideal—the greater

is the need for statistical methods. Experiment is most perfect in the case of physics and chemistry. Here the influence of disturbing causes is usually small, though not negligible. In biology—in many instances at least—experiment is inevitably much less perfect. The external conditions are much more difficult adequately to control; the internal conditions of either plants or animals are largely beyond control, and beyond even such observations as may enable us, if we so desire, to select a series of similar individuals. Experimental work, therefore, on plants or animals—work, for example, in physiology, genetics, or psychology—is, as a rule, very far from attaining the experimental ideal: a residuum of disturbing causes is nearly always troublesome.

For another moral, let the experimenter who is driven to use statistical methods not forget this, that the very fact that he is compelled to use statistical methods is a reflection on his experimental work. It shows that he has failed to attain the very object of experiment to exclude disturbing causes. He should ask himself at every stage: Are these disturbing causes really inevitable? Can I in no way eliminate them or reduce their influence? It is often the case (e.g., in biology) that the experimental worker shows a certain, indeed a strong, prejudice against statistical work. From the present standpoint his attitude is natural and right, so long as perfect experiment or nearly perfect experiment is possible. But where this is no longer the case the attitude ceases to be justifiable. Statistical methods afford the only hope of progress.

A. Prerequisites to the application of statistical methods. Before applying the statistical method to observed data the physiologist should carefully scrutinize the units of measure, the material studied, and the technique used in the experiment. He also needs to comprehend the significance of a frequency distribution and have a working knowledge of the probable error concept.

1. Scrutiny of the units of measure. If the physiologist desires to use the statistical tool in a particular instance, he must satisfy himself that the units of measure with which his experimental work is concerned are adequate for the purpose of answering the question which he is attempting to solve. Most of the criticism by the physiologist against statistical studies is directed at failure of the statistical worker to evaluate the goodness of his observed facts. Usually the physiological problem is directed at some general concept; such as cardiac reserve, growth of the child, metabolism of the cell, heredity, etc. Cardiac reserve is measured in terms of pulse beats, blood pressure, electrocardiograms; the growth of the child, in terms of stature and body weight; the metabolism of the cell, in terms of gaseous exchange; the heredity of mice in terms of inherited characteristics. These facts which are observed and counted might be good or poor with reference to measuring the abstract concept in which the physiologist is interested. For instance, a pound of weight and an inch of height are both definite

concepts of measure. The increase in one pound of weight or in one inch of height in a child, age 3, are measures of growth. One might ask —do these increases in weight and height stand for the same abstract ideas in the child as they would if they had occurred in the parent? Obviously the biological significance of the increase in weight and height varies with reference to abstract concepts, such as growth, nutrition, build, etc., which they are presumed to measure. Suppose that one considers the increase of weight in a child from 3 to 4 years as a certain per cent of its adult weight and the increase in height for the same age interval as a per cent of the adult height, these two per cents are not identical with reference to the abstract ideas of growth, nutrition and build. Increase in height is largely a measure of bony development while increase in weight is a complex index of mass development, build and nutrition. Consequently, it is wrong to say that "the growth of the child is proceeding at a certain rate in this age interval," the statement must be that "the growth of the child, in so far as it is measured in terms of body weight, or body height, is proceeding at a certain rate in this age interval."

2. Scrutiny of the material used. The homogeneity of a group of experimental animals is always a matter of considerable importance to the physiologist. He is particularly concerned that his control animals correspond as closely as possible with those upon which he is attempting to solve a physiological problem. Varying degrees of homogeneity among laboratory animals are required by different types of physiological experiments. In many cases it is sufficient that the control group consist of animals in the same species and approximately the same age as those which are subjected to experimentation. When the problems of physiology merge into those of immunology it is frequently necessary to obtain animals with a similar genetic pattern. In a statistical analysis of such a problem it is a prime essential to determine whether or not the objects of experimentation are representative samples from a single universe of facts. Samples which represent several universes must not be used for intercomparisons. Whenever such items as sex, age, exposure to disease, diet, weight, activity, racial stock, etc., can make any difference in the experimental conclusions, the control and experimental groups must be as nearly identical as possible in all such characteristics.

3. Scrutiny of technique. A statistical analysis of physiological data is usually not primarily concerned with a high degree of accuracy in physiological technique. However, technique must always be sufficiently accurate to measure the objects of experimentation within their

natural or physiological variability. For example, the means, the standard deviations and other frequency constants of hemoglobin determinations by the Newcomer method upon a hundred individuals could be determined with almost the same degree of accuracy if the measurements were read in grams of hemoglobin per 100 cc. as if the readings were in milligrams per 100 cc. The inefficiency of coarse grouping is practically eliminated by large numbers of observations.

This is not true, however, if biased errors are present in the measurements. If the hemoglobin scale is faulty, for instance, the total error might be considerable. Constant errors must be weeded out by consideration of improvement in experimental technique. Accidental

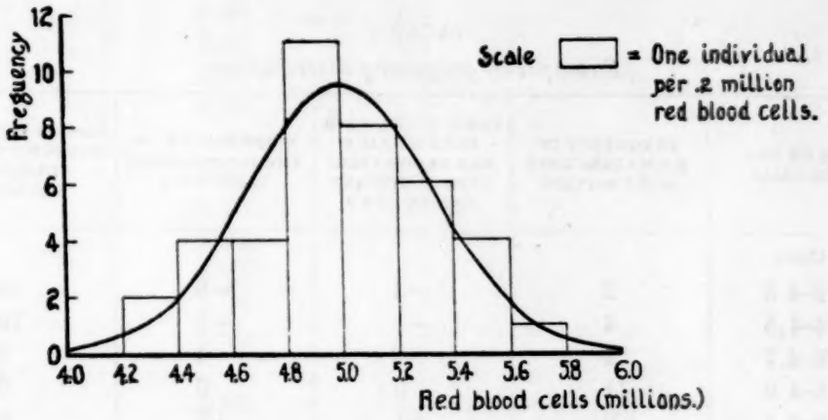

Fig. 1. Bar diagram of frequency distribution of red blood cell counts in 40 normal individuals.

errors for the most part can be evaluated by the so-called normal curve of errors which will be considered later in the discussion.

4. Frequency distribution. After a statistical series of data is accumulated by observing corresponding facts upon homogeneous material, the easiest way in which to comprehend the data as a series is to arrange them in the form of a frequency distribution.

In table 1 a sample distribution is given of Haden's data (244, p. 770) on normal red blood cells. A diagram of such a frequency distribution is usually represented as a bar diagram as shown in figure 1.

Computation technique for mean and standard deviation. Proportionate first moment about arbitrary origin =

$$\nu_1 = \frac{+18}{40} = 0.45 \text{ (class units)} = 0.09 \text{ million red blood cells}$$

Proportionate second moment about arbitrary origin =

$$\nu_2 = \frac{122}{40} = 3.05 \text{ (class units)}$$

(actual units = 0.2 times class units)

M = mean = average = arbitrary origin $+ 0.2\,\nu_1 = 4.99$ red blood cells millions

σ (sigma) = standard deviation = $\sqrt{\text{second moment about mean}}$ =

$\sqrt{\nu_2 - (\nu_1)^2} = \sqrt{3.05 - 0.2025} = \sqrt{2.8475} = 1.68745$ class units or

0.3375 red blood cells (millions)

TABLE 1

Example of frequency distribution

RANGE OF RED BLOOD CELLS	FREQUENCY IN EACH CLASS UNIT OF 0.2 MILLION	CLASS UNITS, EACH IS 0.2 MILLION RED BLOOD CELLS WITH ARBITRARY ORIGIN AT 4.9	FIRST MOMENT = FREQUENCY TIMES CLASS UNIT	SECOND MOMENT = FREQUENCY TIMES CLASS UNIT SQUARED
millions				
4.2–4.3	2	−3	−6	18
4.4–4.5	4	−2	−8	16
4.6–4.7	4	−1	−4	4
4.8–4.9	11	0	0	0
5.0–5.1	8	+1	+8	8
5.2–5.3	6	+2	+12	24
5.4–5.5	4	+3	+12	36
5.6–5.7	1	+4	+4	16
Total.....	40		+18	122

Probable error of this distribution = 0.6745σ = 0.2276 red blood cells (millions).

The computation of many statistical constants is simplified by computing in frequency groups. The effect of frequency grouping upon the statistical result is usually negligible. Direct and group computation of the average in Haden's data is as follows:

Direct and group computation of average

RANGE OF RED BLOOD CELLS	OBSERVED RED BLOOD CELL COUNTS	RED BLOOD CELL COUNTS TAKEN AT MEDIAN OF CLASS INTERVAL	FREQUENCY IN EACH CLASS UNIT OF 0.2 MILLION	FREQUENCY TIMES MEDIAN OF CLASS UNIT
millions	*millions*	*millions*		
4.2–4.3	4.27	4.3	2	8.6
	4.32	4.3		
4.4–4.5	4.40	4.5	4	18.0
	4.52	4.5		
	4.56	4.5		
	4.58	4.5		
4.6–4.7	4.64	4.7	4	18.8
	4.70	4.7		
	4.72	4.7		
	4.73	4.7		
4.8–4.9	4.80	4.9	11	53.9
	4.80	4.9		
	4.80	4.9		
	4.80	4.9		
	4.84	4.9		
	4.87	4.9		
	4.89	4.9		
	4.93	4.9		
	4.97	4.9		
	4.98	4.9		
	4.99	4.9		
5.0–5.1	5.00	5.1	8	40.8
	5.02	5.1		
	5.05	5.1		
	5.09	5.1		
	5.09	5.1		
	5.10	5.1		
	5.15	5.1		
	5.16	5.1		
5.2–5.3	5.20	5.3	6	31.8
	5.20	5.3		
	5.20	5.3		
	5.26	5.3		
	5.28	5.3		
	5.36	5.3		
5.4–5.5	5.46	5.5	4	22.0
	5.49	5.5		
	5.50	5.5		
	5.57	5.5		
5.6–5.7	5.62	5.7	1	5.7
Total.....	198.91	199.60	40	199.6
Average.....	4.973	4.990		4.99

Three simple and highly efficient constants which give a general description of a frequency distribution are the average, standard deviation and the probable error. The calculation of the standard deviation (σ) is shown in table 1. The formula of standard deviation is as follows:

$$\sigma = \sqrt{\frac{\text{sum of the squared deviations from mean}}{\text{number of observations}}} = \sqrt{\frac{\Sigma (\bar{x})^2}{n}}$$

The probable error and standard deviation are the same kind of measures and consequently have a constant relationship to each other:

$$\text{Probable error} = 0.6745\sigma$$

A nomogram of this relationship will be found on page 341.

When frequency distributions are based on small samples and contain coarse grouping effects, there is a considerable amount of variation between the bars of such diagrams as illustrated in figure 1. If the number of observations is large and the groups quite small, the distribution would approach a smooth curve (such as the one drawn). In order to be a good fit to the observed frequencies such a theoretical curve must contain between it and the abscissa a total area which is equivalent to that of the observed bars of frequency. Also the areas for every class interval under the theoretical curve must be proportionately equivalent to the corresponding observed bars.

If the distribution is markedly asymmetrical, measures of skewness must be calculated in order to obtain a more complete description. Ordinarily this will not be necessary in most physiological problems. It is essential to realize that the mean and standard deviation are only two of the descriptive facts about this distribution. If one should take the distribution as indicated in the bar diagram, cut out a piece of card board similar to it, and then attempt to balance the abscissa of the card board on a knife edge the mean would represent the center of gravity and the σ the radius of gyration of the distribution. Consequently, these two descriptive constants are simple concepts which the mind finds easy to grasp.

5. The probable error concept. Computation of simple constants is usually sufficient to describe statistical data. However, descriptions of statistical data are often made upon small samples. The desire to go further than description arises from deep rooted belief of scientists in the existence of order and arrangement in phenomena observed in nature. "In the first place," says Whitehead (659, p. 5) "there can be

no living science unless there is a widespread instinctive conviction in the existence of an *Order of Things*, and, in particular, of an *Order of Nature*." This belief leads directly to the concept of sampling. If there is an order of things, it is assured that there will be a degree of stability in the results obtained from successive samples. If this were not true, no significance could be attached to any study except one which included the entire universe of corresponding facts.

Obviously the physiologist performs an experiment from which he intends to draw inferences with respect to the universe of all similar experiments performed in the future. The words "universe" or "population" are designated as the conventional terms to indicate the type of data from which a certain sample has been drawn. The experimenter naturally assumes that his particular sample is a good one and representative of the universe about which he is talking. With reference to the example on blood counts it is reasonable to suppose that the 40 individuals were normal in every respect and representative of the universe. Yet the theory of sampling states that sometimes a sample of 40 will be drawn which will not be representative and the present sample has a chance of being the unusual and non-representative one. To be sure it is true that the physiologist is more likely to draw an ideal sample from the universe of facts which he is studying than he is to draw one which deviates widely. As he performs a considerable number of experiments he feels a corresponding increase in certainty that his results represent an ideal sample. Consequently, he is able to draw general inferences with greater boldness and a sense of security.

The application of the probable error concept to practical laboratory problems enables the investigator to know how much experimental work must be done in order to obtain a measured degree of security. Not only does the probable error concept offer a solution for such sampling problems but it does so with economy of effort. It enables one to use comparatively small numbers of representative data and establish conclusions approximating those obtained by a very large study from the same kind of data. Since physiological statistics are frequently difficult to obtain, the application of the probable error concept to problems in this subject is especially desirable.

The formulae for probable error arise from consideration of the so-called normal curve of errors. Other names for it are the normal frequency distribution, the Gaussian Curve, the LaPlace Curve, the De-

Moivre Curve, the Law of Chance, or simply the normal curve. The normal curve is expressed as the following function:

$$y = \frac{n}{\sqrt{2\pi}\,\sigma} e^{-\frac{\bar{x}^2}{2\sigma^2}}$$

in which y is frequency, $\bar{x}$ is the variable factor with which the investigator is concerned expressed in deviation from its average value, σ is the standard deviation of x, and e and π are the two well-known constants 2.71828 and 3.1416, respectively.

The normal curve is particularly useful because of its wide application in many subjects. It describes the variation in many biological, physiological, anthropological and sociological subjects. It evaluates the variation in chance experimental errors and is the limit of the point binominal, an expression involving probabilities in the form of combinations.

Since the normal curve is a frequency distribution, the average and the standard deviation can be computed as indicated in table 1. A set of normal curves is pictured in figure 2. Obviously the curve is symmetrical. The mean is at the mid-point of the distribution (fig. 2a) and divides the total area into two equal parts. The boundary lines of plus or minus one probable error from the mean value include half of the total area between them (fig. 2b). If the distance of two probable errors is measured on each side of the mean (fig. 2c) 82.26 per cent of the total area of the normal curve will lie within these limits. The boundaries of plus and minus three probable errors from the mean of the normal curve include within them 95.70 per cent of the total frequency. The total area under the normal curve can be expressed in terms of standard deviation quite as easily as those of probable error. The limits of plus or minus one standard deviation from the mean enclose 68.26 per cent of the area and those for plus or minus two times standard deviation 95.45 per cent (figs. 2*e* and *f*). Standard deviation and probable error are the same type of measures and, consequently, they have a constant relationship to each other.

$$\text{Probable error} = 0.6745\sigma$$

Since these terms are corresponding units of measure only probable error will be used hereafter in the discussion.

Because the normal curve has a very wide application, it is desirable to adequately describe the area beneath the curve between any set of abscissal limits. Such a procedure saves much labor in applying the

normal areas to the great number of observed frequency distributions which it fits with reasonable accuracy. Tables of area under a normal curve have been published by many different authors; an abbreviated table is given near the end of this paper, page 341. All tables of the probability integral express the area within specified limits as a proportion of the total area which is considered to be unity. Since standard

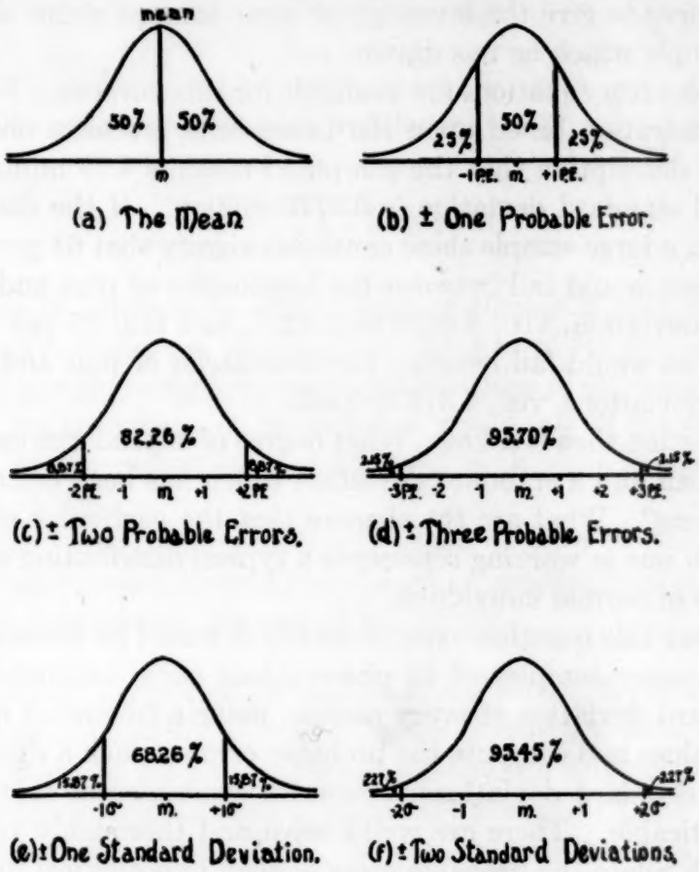

Fig. 2. Subdivisions of the area under a normal curve by probable error and standard deviation limits.

deviation is usually given in some absolute unit, such as red blood cells in our example, the measure of deviation from the mean (in red blood cells) must be given in terms of σ (which also is in terms of red blood cells). Consequently, the limits for any portion of the normal curve are defined in terms of $\frac{\bar{x}}{\sigma}$ i.e., $\frac{\text{deviation from mean}}{\text{standard deviation}}$. The abbreviated table of deviations on page 341, define the proportionate area outside of

plus and minus variations from the mean in terms of $\frac{\bar{x}}{\sigma}$. For practical work a more complete table than this is rarely necessary.

By means of the average, standard deviation and number of observations, the distribution of the area under the normal curve is completely defined. The next important step consists in applying the areas of the normal curve to give the investigator some concept about the goodness of the sample which he has drawn.

Probable error equations are available for this purpose. For instance, in the illustration based upon red blood cells, we have observed as a matter of description that the computed mean is 4.99 millions and the calculated standard deviation is 0.3775 million. If the distribution is made from a large sample these constants signify that 68 per cent of the observations would fall between the boundaries of plus and minus one standard deviation, viz., 4.6525 to 5.3275, and that 95 per cent of the observations would fall between the boundaries of plus and minus two standard deviations, viz., 4.315 to 5.665.

The question then is asked—What degree of dependence can one place upon a mean and a standard deviation which has been calculated from only 40 cases? What are the chances that the particular sample of 40 with which one is working represents a typical distribution of red blood cell counts in normal individuals?

To answer this question experimentally it would be necessary for one to obtain many samples of 40 observations each, calculate the mean and standard deviation of every sample, make a frequency distribution of these values and compute the probable error of such a distribution of means or standard deviations. Such an experimental solution would be impracticable. There are well-known and thoroughly tested equations which relate the probable error of such hypothetical distributions of computed constants to the number of observations and the standard deviation of the observed sample.

If,

σ = standard deviation of the observed material (in example 0.3375 million red blood cells)

and, if,

M = mean of observed material (in example 4.99 million red blood cells)

and,

n is the frequency (in example 40 cases)

then,

$$\text{the probable error of mean} = \text{P.E.}_m = 0.6745\left(\frac{\sigma}{\sqrt{n}}\right) = (0.6745)\left(\frac{0.3375}{\sqrt{40}}\right) =$$

$$(0.6745)\left(\frac{0.3375}{6.3246}\right) = 0.036$$

Likewise,

$$\text{the probable error of the standard deviation} = 0.6745\left(\frac{\sigma}{\sqrt{2\,n}}\right) = 0.6745$$

$$\left(\frac{0.3375}{\sqrt{80}}\right) = 0.02543$$

The degree of dependence which the investigator is able to place in such an observed mean is indicated by the size of its probable error. If he should sample many frequency distributions of 40 cases, he could expect that the true mean of the universe would fall 50 per cent of the time within the boundary lines of plus and minus one probable error, viz., 4.954 to 5.026.

The limitations in the application of probable error equations due to the assumptions upon which they are based are summarized in the table of statistical equations at the end of this article.

B. The use of statistics as a laboratory tool. Since experiment is the vital element in the development of physiology as a science, it is very important to see how statistical method can help out the investigator to a better comprehension of his routine results.

1. Description of measured data. In order to obtain a mental picture about a set of complex data, detailed enumeration must be replaced by comparatively simple descriptive constants which can be visualized. To be sure, computed constants will practically never contain all the details which exist in the original observations. However, this limitation in description is an advantage rather than a drawback since it is multiplicity of detail which confuses the mind and makes it impossible to grasp a clean-cut picture of the important facts in the data *en masse*.

The bulk of physiological data can be roughly pictured by comparatively simple statistical constants. Frequency distributions can usually be sufficiently described by the computation of a mean and standard deviation. Most bivariant data are in the form of simple linear corre-

lation and can be evaluated by correlation coefficients. These three constants need to be computed in a great variety of physiological prob-

TABLE 2

Data of Haden on red blood cell counts, red blood cell volume and hemoglobin

MEN								WOMEN			
Age	Red blood cells	Hemoglobin	Volume of red blood cells	Age	Red blood cells	Hemoglobin	Volume of red blood cells	Age	Red blood cells	Hemoglobin	Volume of red blood cells
	millions	*grams per 100 cc.*	*per cent*		*millions*	*grams per 100 cc.*	*per cent*		*millions*	*grams per 100 cc.*	*per cent*
18	4.93	16.20	45.0	30	4.80	15.10	46.5	20	4.15	13.20	38.0
18	5.10	16.20	48.0	30	4.73	13.80	44.0	21	3.89	12.12	36.0
19	5.20	15.75	45.0	31	4.40	14.41	43.0	22	4.20	13.10	38.0
23	4.80	16.08	45.5	32	5.20	16.10	45.0	23	4.40	13.50	40.5
23	5.62	16.61	51.0	32	5.02	15.52	46.0	25	4.45	13.88	41.0
24	4.87	15.13	45.5	32	4.80	15.11	46.0	26	4.38	14.80	43.0
25	4.84	15.00	42.0	33	4.58	14.50	45.0	27	4.72	14.60	43.0
25	5.26	16.40	49.0	35	5.05	15.45	46.0	27	3.97	11.90	37.0
25	5.49	16.70	49.5	35	5.15	16.50	48.0	30	4.56	14.00	41.0
25	5.50	16.05	50.0	35	5.46	16.15	49.0	38	3.95	12.10	37.0
26	5.36	16.10	47.0	35	4.97	15.40	45.0	40	4.31	13.40	40.0
26	4.98	16.32	47.0	36	4.80	15.40	45.0	40	4.26	13.50	39.0
26	5.00	16.40	45.0	38	4.27	14.00	39.5				
27	4.70	14.72	46.0	39	5.16	16.10	47.5				
28	5.57	17.17	51.0	40	4.64	14.30	42.0				
28	5.09	15.53	45.0	44	5.20	16.90	49.0				
28	4.72	14.70	44.0	44	4.56	14.20	42.0				
29	5.09	15.80	46.0	49	4.32	14.00	40.0				
29	4.52	14.02	44.0	50	4.89	15.60	44.5				
29	4.99	15.70	46.0	50	5.28	16.10	48.0				

(There were 21 corresponding sets of observations for a group of people diagnosed pernicious anemia. The sex and age were not given in this abnormal group.)

0.74	2.76	10.0	1.68	6.20	18.5	2.27	5.95	37.0
1.24	2.63	15.0	1.73	5.89	22.0	2.33	9.08	28.5
1.38	4.65	15.0	1.75	7.35	21.0	2.60	7.60	28.0
1.42	6.65	19.5	1.81	6.15	22.0	2.79	10.20	32.0
1.58	6.80	21.0	1.88	9.22	29.0	2.93	12.90	36.5
1.64	7.13	21.0	1.99	8.20	26.0	3.33	12.20	37.0
1.61	5.60	18.0	2.10	8.59	25.0	1.94	7.28	24.5

lems. Consequently, an example of computation technique is given in tables 3 and 4, and the original data in table 2.

TABLE 3

Correlation of hemoglobin and red blood cells in males

	NORMAL MALES GRAMS OF HEMOGLOBIN PER 100 CC.								f = FREQUENCY OF RED BLOOD CELLS IN EACH CLASS UNIT 0.2 MILLION	y = RED BLOOD CELLS CLASS UNITS 0.2 MILLION ARBITRARY ORIGIN 4.9	f TIMES (y)	f TIMES $(y)^2$	FX_y	$y\,(FX_y)$
	13.5 to 13.9	14.0 to 14.4	14.5 to 14.9	15.0 to 15.4	15.5 to 15.9	16.0 to 16.4	16.5 to 16.9	17.0 to 17.4						
Red blood cells (millions):														
4.2–4.3	–	2	–	–	–	–	–	–	2	−3	−6	+18	−4	+12
4.4–4.5	–	3	1	–	–	–	–	–	4	−2	−8	+16	−7	+14
4.6–4.7	1	1	2	–	–	–	–	–	4	−1	−4	+4	−7	+7
4.8–4.9	–	–	–	6	2	3	–	–	11	0	0	0	+8	0
5.0–5.1	–	–	–	1	3	3	1	–	8	+1	+8	+8	+12	+12
5.2–5.3	–	–	–	–	1	4	1	–	6	+2	+12	+24	+12	+24
5.4–5.5	–	–	–	–	–	2	1	1	4	+3	+12	+36	+11	+33
5.6–5.7	–	–	–	–	–	–	1	–	1	+4	+4	+16	+3	+12
F = frequency of Hb. in class unit of 0.5 gram per 100 cc	1	6	3	7	6	12	4	1	40 = n or size of sample		Total $f(y)$ = +18	Total $f(y)^2$ = 122	Total FX_y = +28	Total $y(FX_y)$ = +114
X = Hb. class unit 0.5 gram per 100 cc	−3	−2	−1	0	+1	+2	+3	+4						
F times X	−3	−12	−3	0	+6	+24	+12	+4	Total FX = +48					
F times $(X)^2$	+9	+24	+3	0	+6	+48	+36	+16	Total $F(X)^2$ = +142					

The arbitrary origin of x = 15.25 grams of hemoglobin/100 cc.
The arbitrary origin of y = 4.9 red blood cells in millions.
The proportionate moments in class units about these arbitrary origins are:

$\nu_{1x} = \frac{28}{40} = 0.7$
$\nu_{2x} = \frac{142}{40} = 3.55$
The mean of x = arbitrary origin + ν_{1x} in actual units = 15.25 + (0.7) (0.5) = 15.6
μ_{2x} = The second moment about mean $= \nu_{2x} - (\nu_{1x})^2 = 3.55 - .49 = 3.06$
$\sigma_x = \sqrt{\mu_{2x}} = \sqrt{3.06} = 1.7493$ in class units
$\therefore \sigma_x$ in actual units = (1.7493) (0.5) = 0.8746

$\nu_{1y} = \frac{18}{40} = 0.45$
$\nu_{2y} = \frac{122}{40} = 3.05$
The mean of y = arbitrary origin + ν_{1y} in actual units = 4.9 + (.45) (.2) = 4.99
μ_{2y} = The second moment about mean $= \nu_{2y} - (\nu_{1y})^2 = 3.05 - 0.2025 = 2.8475$
$\sigma_y = \sqrt{\mu_{2y}} = \sqrt{2.8475} = 1.68745$ in class units
$\therefore \sigma_y$ in actual units = (1.68745) (0.2) = 0.33749

ν_{xy} = The cross-product moment about the arbitrary origin = $\frac{114}{40} = 2.85$
The cross-product moment about means $= \mu_{xy} = \nu_{xy} - (\nu_{1x})\,(\nu_{1y}) = 2.85 - 0.315 = 2.535$
r = correlation coefficient = $\frac{2.535}{2.958184} = 0.8588$

The illustrative data of table 2 were taken from an article by Haden (244). The items measured consist of red blood cell counts in millions, hemoglobin in grams per 100 cc. and hematocrit reading of the volume per cent of red blood cells. His normal data are based upon 40 men and 12 women.

The customary mode of analysis in this type of problem is by the use of ratios, such as color index, volume index and saturation index. R. A. Fisher (99, p. 4) points out the fact that to postulate a ratio of two variables, such as in this case $\frac{\text{RBC}}{\text{Hb}}$ = a constant, might frequently be a poor assumption to make.

The first and simplest descriptive step in the analysis of these data consists of plotting the variables as spot diagrams (figs. 3 a, b, c). Such diagrams aid in the visualization of the problem and often indicate the course of procedure. For instance, in all three graphs the divergence of pernicious anemia from normal cases is apparent; also the non-homogeneity of normal males and females. Moreover, large deviations of atypical cases, such as that indicated by circling in figure 3a, can be allocated.

The next step in the description of the data is the formation of correlation tables illustrated by table 3. The correlation table becomes a most important step in problems which involve large frequencies. The computation of mean, standard deviation and correlation coefficient is indicated on table 3.

When the numbers are small, computation of the mean, standard deviation, and correlation coefficient can be performed upon the original observations without arranging them in grouped frequency distributions or correlation tables. The direct method of computation is illustrated in the following example on normal females, table 4.

In relation to the computation technique as shown by table 4, the means are the first moments ν_{1x}, and ν_{1y} since the arbitrary origin of zero was used in each instance.

Since the data used in this example are few, all constants were determined by direct method in order to eliminate grouping effects inherent in the construction of a correlation table.

TABLE 4

Computation of the correlation coefficient of hemoglobin and red blood cells in 12 normal women

RED BLOOD CELLS	(RED BLOOD CELLS)²	HEMOGLOBIN	(HEMOGLOBIN)²	(RED BLOOD CELLS TIMES HEMOGLOBIN)
millions		*grams per 100 cc.*		
4.15	17.2225	13.20	174.24	54.780
3.89	15.1321	12.12	146.89	47.147
4.20	17.6400	13.10	171.61	55.020
4.40	19.3600	13.50	182.25	59.400
4.45	19.8025	13.88	192.65	61.766
4.38	19.1844	14.80	219.04	64.824
4.72	22.2784	14.60	213.16	68.912
3.97	15.7609	11.90	141.61	47.243
4.56	20.7936	14.00	196.00	63.840
3.95	15.6025	12.10	146.41	47.795
4.31	18.5761	13.40	179.56	57.754
4.26	18.1476	13.50	182.25	57.510
Total 51.24	219.5006	160.10	2,145.67	685.991

Size of sample = $n = 12$

Arbitrary origin for both red blood cells and hemoglobin is zero:

Let x = Red blood cells
Let y = Hemoglobin

$$\text{(Mean) } \nu_{1x} = \frac{51.24}{12} = 4.27 \pm 0.0493 \qquad \text{(Mean) } \nu_{1y} = \frac{160.1}{12} = 13.342 \pm 0.1825$$

$$\nu_{2x} = \frac{219.5006}{12} = 18.291717 \qquad \nu_{2y} = \frac{2145.67}{12} = 178.80583$$

$$\mu_{2x} = \nu_{2x} - (\nu_{1x})^2 = 0.058817 \qquad \mu_{2y} = \nu_{2y} - (\nu_{1y})^2 = 0.80575$$

Standard deviation of $x = \sigma_x = \sqrt{\mu_{2x}} = 0.2425 \pm 0.0349$

Standard deviation of $y = \sigma_y = \sqrt{\mu_{2y}} = 0.8976 \pm 0.1291$

$$\nu_{xy} = \frac{685.991}{12} = 57.165917$$

$$\mu_{xy} = \nu_{xy} - (\nu_{1x})\,(\nu_{1y}) = 57.165917 - 56.968931 = + 0.196986$$

Correlation coefficient $= r_{xy} = \dfrac{\mu_{xy}}{\sigma_x\,\sigma_y} = \dfrac{+ 0.196986}{0.217668} = + 0.9050 \pm 0.0386$

The probable errors of the means were computed by the formula:

$$^{2}\text{Probable error of mean} = 0.6745\,\frac{\sigma}{\sqrt{n-1}}$$

The probable errors of the standard deviations were computed by the formula:

$$^{2}\text{Probable error of standard deviation} = 0.6745\,\frac{\sigma}{\sqrt{2\,(n-1)}}$$

The probable error of the correlation coefficient was computed by the formula:

$$^{2}\text{Probable error of correlation coefficient } (r) = 0.6745\,\frac{(1-r^2)}{\sqrt{(n-2)}}$$

The descriptive constants which were computed by the direct method from these data are summarized as follows:

(Red blood cells = 1; hematocrit volume of red blood cells = 2; hemoglobin = 3)

		NUMBER OF CASES	MEAN $\pm$ P.E.$_m$	STANDARD DEVIATIONS $\pm$ P.E.$_\sigma$	CORRELATION COEFFICIENT $\pm$ P.E.$_r$
Normals	Men	40	$M_1 = 4.973 \pm 0.0358$	$\sigma_1 = 0.3317 \pm 0.0253$	$r_{12} = 0.8813 \pm 0.0244$
			$M_2 = 45.81 \pm 0.285$	$\sigma_2 = 2.638 \pm 0.2015$	$r_{13} = 0.8685 \pm 0.0269$
			$M_3 = 15.53 \pm 0.0954$	$\sigma_3 = 0.8835 \pm 0.0675$	$r_{23} = 0.8212 \pm 0.0356$
	Women	12	$M_1 = 4.27 \pm 0.0493$	$\sigma_1 = 0.2425 \pm 0.0349$	
			$M_2 = 39.46 \pm 0.4535$	$\sigma_2 = 2.23 \pm 0.3207$	
			$M_3 = 13.34 \pm 0.1825$	$\sigma_3 = 0.8976 \pm 0.1291$	
Pernicious anemia group	With circled case, fig. 3	21	$M_2 = 24.119 \pm 1.094$	$\sigma_2 = 7.250 \pm 0.773$	
			$M_3 = 7.287 \pm 0.379$	$\sigma_3 = 2.513 \pm 0.268$	$r_{23} = 0.8283 \pm 0.0486$
	Without circled case, fig. 3	20	$M_1 = 1.9235 \pm 0.932$	$\sigma_1 = 0.6023 \pm 0.0659$	$r_{12} = 0.9563 \pm 0.0136$
			$M_2 = 23.475 \pm 1.055$	$\sigma_2 = 6.818 \pm 0.746$	$r_{13} = 0.9066 \pm 0.0283$
			$M_3 = 7.354 \pm 0.3955$	$\sigma_3 = 2.556 \pm 0.2797$	$r_{23} = 0.9609 \pm 0.0122$

It is often very desirable to extend the description of a problem of this type by obtaining the linear equations which best describe one variable in terms of the averages of the other. These equations come directly from a knowledge of means, standard deviations and correla-

[2] Since the total frequency is small, $n - 1$, and $n - 2$ respectively are used in the equations for probable errors of the mean, standard deviation and correlation coefficient, in order to correct for the limitation in degrees of freedom. (For further explanation see Fisher 185, 189 and 190.)

tion coefficients. The variable with a bar over it represents the one to be calculated.

For example: In the group of normal men the equation expressing red blood cells (RBC) in terms of the variable per cent volume of red blood cells (V), is obtained as follows:

$$\overline{\text{RBC}} - \text{Mean}_{\text{RBC}} = (r_{\text{RBC},V}) \left[\frac{\text{RBC}}{\sigma_V}\right] (V - \text{mean}_V)$$

Since,

Mean of RBC = 4.973; $\sigma_{\text{RBC}} = 0.3317$; $\text{Mean}_V = 45.81$; $\sigma_V = 2.638$; and $r_{\text{RBC},V} = 0.8813$

By substitution,

$$\overline{\text{RBC}} - 4.973 = (0.8813) \left[\frac{0.3317}{2.638}\right] (\text{Vol.} - 45.81)$$

$\therefore$ Red blood cells (millions) = 0.1108 volume (%) − 0.1034

The various possible linear relations of the three variables in the normal male and pernicious anemia bloods are as follows:

Normal group of 40 men	Red blood cells	=	0.1108	(Volume)	−0.1034
	Volume	=	7.009	(Red blood cells)	+10.95
	Red blood cells	=	0.3261	(Hemoglobin)	−0.0908
	Hemoglobin	=	2.313	(Red blood cells)	+4.03
	Volume	=	2.452	(Hemoglobin)	+7.73
	Hemoglobin	=	0.2750	(Volume)	+2.93
Pernicious anemia group (20 cases)	Red blood cells	=	0.08453	(Volume)	−0.0609
	Volume	=	10.825	(Red blood cells	+2.653
	Red blood cells	=	0.2136	(Hemoglobin)	+0.3524
	Hemoglobin	=	3.847	(Red blood cells)	−0.0464
	Volume	=	2.563	(Hemoglobin)	+4.626
	Hemoglobin	=	0.3602	(Volume)	−1.1024

These equations are represented graphically in figure 3 a, b, c,

2. The significance of differences between the means, standard deviations, and correlation coefficients of two samples. Thus far in the description of these data on normal and pernicious anemia bloods, three objects have been gained: first, a partial description of the frequency distribution in terms of means and standard deviations; second, a description of the relation between any two variables by correlation coefficients and regression lines, and third, the establishment of the approximate degree of goodness with which these constants have been sampled out of an infinite universe of like constants by the calculation of their probable errors.

In practical analysis it is very convenient to be able to estimate how different any two constants might be from each other. To do this

the probable error of the difference can be calculated if the probable errors of the two constants to be compared are known.

First example:

Mean of red blood cells$_{\text{Normal}}$ $= 4.973 \pm 0.0358$

Mean of red blood cells$_{\text{P.A.}}$ $= 1.9235 \pm 0.0932$

Difference between means $= 3.0485$

Probable error of this difference $= \sqrt{(\text{P.E.}_{\text{Normal}})^2 + (\text{P.E.}_{\text{P.A.}})^2} = \sqrt{(0.0358)^2 + (0.0932)^2} = 0.09936$

Second example:

Standard deviation of red blood cells$_{\text{Normal}}$ $= 0.3317 \pm 0.0253$

Standard deviation of red blood cells$_{\text{P.A.}}$ $= 0.6023 \pm 0.0659$

Difference between the standard deviations $= 0.2706$

Probable error of this difference $= \sqrt{(0.0253)^2 + (0.0659)^2} = 0.0706$

Third example:

Correlation of red blood cells and hemoglobin$_{\text{Normal}}$ $= 0.1644 \pm 0.0180$

Correlation of red blood cells and hemoglobin$_{\text{P.A.}}$ $= 0.2541 \pm 0.0404$

Difference between these correlations $= 0.0897$

Probable error of this difference $= \sqrt{(0.018)^2 + (0.0404)^2} = 0.0442$

The interpretation of differences depends upon the assumption of a hypothetical normal distribution of differences. The mean of such an imaginary distribution of normal differences is presumed to be zero. Consequently, the difference obtained between two samples represents the deviation from the mean in such a distribution of differences. If the distribution of differences be normal, the

$$\frac{\text{Deviation from mean}}{\text{Standard error of difference}} = \frac{\bar{x}}{\sigma}$$

The area under the normal curve beyond the limit of $\pm \frac{\bar{x}}{\sigma}$ is tabled on page 341. If the hypothetical distribution of differences can be expressed as a normal curve, it is comparatively easy to obtain an approximate measure of the chance of getting a difference greater than $\pm \frac{\bar{x}}{\sigma}$ by the process of sampling. For instance, if the area outside of these boundaries of $\pm \frac{\bar{x}}{\sigma}$ is 1 per cent of the total frequency, the chances of obtaining a deviation as great as the one observed would occur as a sampling process only once in a hundred times. Consequently, the converse statement can be made "it is probable that the difference is a real one, viz., one not due to sampling but to some extraneous cause."

This test of significance is a practical one and works in almost all instances with considerable precision. The physiologist who is constantly attempting to discern differences between experimental and control groups and to establish the significance of such differences, will find that it is a most useful tool with wide scope in its application.

For illustration, this rule was applied to the problem on blood counts, volume and hemoglobin. Graphically (figs. 3a, b, c,) the homogeneity of the observations made on males and females seems to be in doubt. Haden places males and females into one composite norm disregarding divergence between the sexes. By testing the significance of differences the following values were obtained:

	MEN	WOMEN	DIFFERENCE + P.E.diff.	$\frac{\bar{x}}{\sigma_{diff.}}$	PROBABILITY
					per cent
Mean R.B.C. ± P.E.M.	4.973±0.0358	4.270±0.0493	0.703±0.0609	7.79	0
Mean Hb. ±P.E.M.....	15.53 ±0.0954	13.34 ±0.1825	2.19 ±0.206	7.17	0
Mean Hematocrit Volume ± P.E.M....	45.81 ±0.0285	39.46 ±0.4535	6.35 ±0.4544	9.4	0

Obviously the difference between men and women is so large that it supersedes any likelihood of arising as a sampling difference.

Another use of the equation is seen by testing the homogeneity of the atypical case in the pernicious anemia group (fig. 3a). The various constants were computed with the atypical case kept in the computation and then re-computed with the atypical case discarded. The difference between the two computations was then compared in light of the probable error of the difference.

	PERNICIOUS ANEMIA GROUP INCLUDING ATYPICAL CASE	PERNICIOUS ANEMIA GROUP EXCLUDING ATYPICAL CASE	DIFFERENCE	$\frac{\bar{x}}{\sigma_{diff.}}$	PROBABILITY
					per cent
Mean hemoglobin...	7.287±0.3790	7.354±0.3955	0.067 ±0.548	0.008	99.0
Mean volume.....	24.119±1.094	23.475±1.055	0.644 ±1.52	0.286	77.0
Correlation between Hemoglobin and Volume.....	0.8283±0.0486	0.9609±0.0122	0.1326±0.050	1.78	7.0

The difference between the correlation coefficient computed with and without the atypical case is 0.1326 ±0.0501, a difference which would arise by sampling only seven times in a hundred. Since this analysis

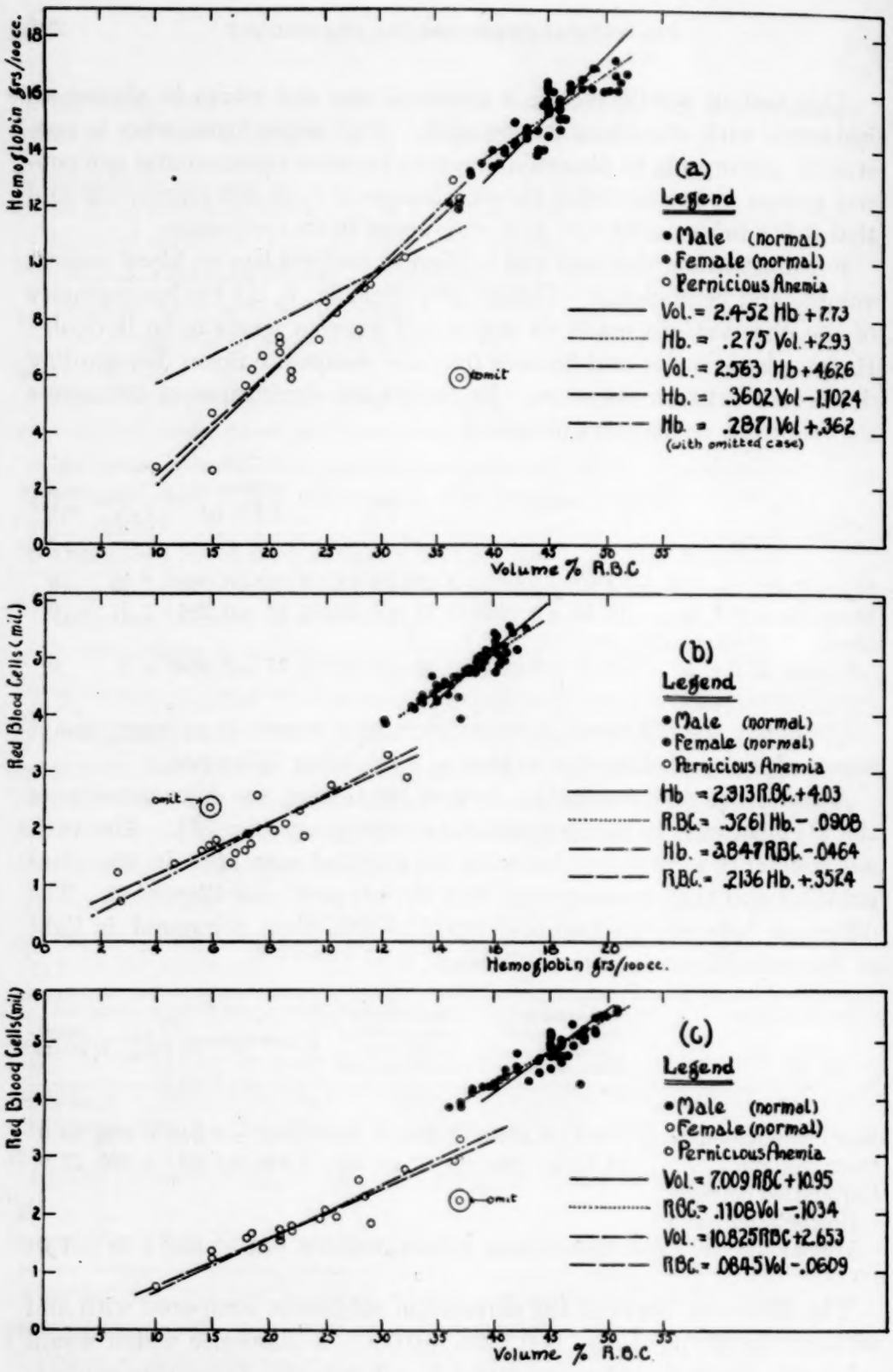

Fig. 3. Spot diagrams of relationship between hemoglobin, red blood cell count and hematocrit reading of volume per cent red blood cells.

is based upon relatively few data, it is better to omit such an observation from the computation (although it should never be discarded or omitted from the original protocols). If the equation representing hemoglobin

TABLE 5

Summary of differences between the normal men and pernicious anemia patients with respect to red blood cell counts, red blood cell volume, and hemoglobin

Legend: Red blood cell counts = 1, red blood cell volume = 2, hemoglobin = 3, M = mean, σ = standard deviation, r = correlation coefficient.

TYPE OF CONSTANT	NORMAL MEN		PERNICIOUS ANEMIA		DIFFERENCE BETWEEN NORMAL AND PERNICIOUS ANEMIA		
	Value ± its probable error	Per cent which σ of higher order is of σ zero order	Value ± its probable error	Per cent which σ of higher order is of σ zero order	Value of difference ± probable error of difference	Differences divided by σ of differences	Percentage probability of such a difference by (chances per 100) sampling
M_1	4.973 ±0.0358	—	1.924 ±0.0932	—	3.049 ±0.0998	30.6	0.0
M_2	45.81 ±0.285	—	23.48 ±1.055	—	22.33 ±1.093	13.8	0.0
M_3	15.53 ±0.0954	—	7.354 ±0.3955	—	8.176 ±0.4068	13.6	0.0
σ_1	0.3317±0.0253	100	0.6023±0.0659	100	0.2706±0.0706	2.59	1.0
σ_2	2.638 ±0.2015	100	6.818 ±0.746	100	4.180 ±0.7727	3.65	0.02
σ_3	0.8835±0.0675	100	2.556 ±0.2797	100	1.6725±0.2877	3.92	0.008
$\sigma_{1.2}$	0.1568±0.0120	47	0.1761±0.0193	29	0.0193±0.0227	0.85	60.0
$\sigma_{1.3}$	0.1644±0.0126	50	0.2541±0.0278	42	0.0897±0.0305	2.94	0.3
$\sigma_{1.23}$	0.1323±0.0101	40	0.1741±0.0191	29	0.0418±0.0216	1.94	5.0
$\sigma_{2.1}$	1.247 ±0.0952	47	1.993 ±0.2181	29	0.746 ±0.2380	3.13	0.2
$\sigma_{2.3}$	1.505 ±0.1149	57	1.888 ±0.2066	28	0.383 ±0.2357	1.62	11.0
$\sigma_{2.13}$	1.211 ±0.0925	46	1.293 ±0.1415	19	0.082 ±0.1690	0.49	38.0
$\sigma_{3.1}$	0.438 ±0.0334	50	1.079 ±0.1181	42	0.641 ±0.1227	5.23	0.000
$\sigma_{3.2}$	0.5042±0.0385	57	0.7078±0.0774	28	0.2036±0.0864	2.36	2.0
$\sigma_{3.12}$	0.4253±0.0325	48	0.6995±0.0765	27	0.2743±0.0831	3.30	0.1
r_{12}	0.8813±0.0244	—	0.9563±0.0136	—	0.0750±0.0279	1.81	7.0
r_{13}	0.8685±0.0269	—	0.9066±0.0283	—	0.0381±0.0391	0.66	51.0
r_{23}	0.8212±0.0356	—	0.9609±0.0122	—	0.1397±0.0376	2.51	1.2
$r_{12.3}$	0.5939±0.0718	—	0.7287±0.0767	—	0.1348±0.1050	0.87	38.0
$r_{13.2}$	0.5366±0.0790	—	−0.1520±0.1598	—	0.6886±0.1783	2.60	0.9
$r_{23.1}$	0.2382±0.1046	—	0.7612±0.0688	—	0.5230±0.1252	2.82	0.5

in terms of red blood cells is calculated with the atypical case included, the regression line does not follow the array of means (fig. 3a).

One of the most helpful applications of the rule for interpretation of significant differences is its use in the comparison of experimental

values with those of corresponding control groups. In the next section, table 5, the normal and pernicious anemia groups are compared in this manner relative to all of their various descriptive constants.

3. Partial correlation and partial standard deviation, as an experimental control. The physiologist will find that the descriptive constants arising from the theory of partial correlation are extremely useful as a practical laboratory tool. Customarily he attempts to evaluate the relation between two or three factors holding certain experimental conditions constant. Partial correlation is a process by which he may take observations on a number of variables and then study the relation between any pair of these variables holding one or more of the other factors constant by statistical methods.

In many instances the experimenter does not have the option of holding factors constant by experimental selection. For instance, in this problem on red blood cells, hemoglobin and red blood cell volume, there is no way in which the hemoglobin per cell, or the cell volume could be kept constant except by partial correlation technique. The correlation between hemoglobin and cell volume in normal individuals is ascertained to be 0.8212 $\pm$0.0356. What would be the degree of relationship between hemoglobin and cell volume if the correlation had been computed upon only those individuals who happened to have identical red blood cell counts? The statistical answer is obtained by the following equation:

$$r_{23.1} = \frac{r_{23} - (r_{12})\ (r_{13})}{\sqrt{(1 - r_{12}^2)}\ \sqrt{1 - r_{13}^2}}$$

in which the subscripts 1, 2, 3 stand for the number of red blood cells, volume of red blood cells and hemoglobin, respectively, and r is the correlation coefficient. The decimal point between the subscripts 3 and 1 in the term $r_{23.1}$ separates the items which are being correlated from that one which is being held constant. In this case $r_{23.1}$ is stated as "the correlation coefficient between red blood cell volume and hemoglobin with the red blood cell count held as a constant factor." It is computed as follows:

$$r_{23.1} = \frac{0.8212 - (0.8813)\ (0.8685)}{\sqrt{1 - (0.8813)^2}\ \sqrt{1 - (0.8685)^2}} = \frac{0.8212 - 0.7654}{\sqrt{0.22331}\ \sqrt{0.24571}} =$$

$$+ \frac{0.0558}{(0.47255)\ (0.49569)} = + \frac{0.0558}{0.234238} = + 0.2382$$

The probable error of $r_{23.1}$ is given by the formula:[3]

$$\text{P.E.}_{r_{23.1}} = 0.6745\left[\frac{1 - r_{23.1}^2}{\sqrt{n - k}}\right] = 0.6745\left[\frac{1 - (0.2382)^2}{\sqrt{40 - 3}}\right] = 0.6745\left[\frac{0.9432608}{6.08276}\right] = 0.1046$$

Therefore,

$$r_{23.1} = \pm 0.2382 \pm 0.1046$$

Very frequently partial correlation is used as a method of finding out how much reduction in the variation of a frequency distribution has been attained if the relations between the particular variable and other variables are taken into consideration. For instance, the standard deviation in the frequency distribution in red blood cell volume (σ_2) is 2.638 ±0.2015 per cent. If the correlation between the number of red blood cells and volume ($r_{12} = 0.8813$) is considered, the standard deviation of red blood cell volume with number of red blood cells held constant ($\sigma_{2.1}$) becomes 1.247.

The relative reduction in variation is given by

$$100\left[\frac{\sigma_{2.1}}{\sigma_2}\right] = \frac{1.247}{2.638} \text{ times } 100 = 47 \text{ per cent}$$

Graphically this signifies (fig. 3a) that the points indicating red blood cell volume vary much less about the trend line which relates cell volume to number of red blood cells, than they do if this trend is not considered.

In a corresponding manner the standard deviation of cell volume with hemoglobin held constant ($\sigma_{2.3}$) is 1.505, the ratio of reduction in variability being 57 per cent.

The standard deviation of cell volume when both the number of red blood cells and hemoglobin are held as constant factors is computed as follows:

$$^4\sigma_{2.13} = \sqrt{(\sigma_2)^2\,(1 - r_{12}^2)\,[1 - (r_{23\,1})^2]} = \sqrt{(2.638)^2\,(1 - 0.8813^2)\,(1 - 0.2382^2)}$$

$$= \sqrt{(6.95904)\,(0.22331)\,(0.94326)} = \sqrt{1.46585} = 1.2107$$

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[3] The general formula for partial correlation is given in 687. The k in the probable error equation signifies the number of degrees of freedom which are limited. The k for any zero order correlation coefficient is two (185) and for each higher order of partial correlation one more limitation to the degrees of freedom is added.

[4] The general equation for any partial σ is given in 687.

The ratio of reduction is $\frac{\sigma_{2.13}}{\sigma_2} = \frac{1.2107}{2.638} = 46$ per cent

The relative variation in cell volume is reduced to 47 per cent if the number of red blood cells are held as constant. By holding constant hemoglobin in addition to the number of red blood cells the per cent reduction in cell volume differs by only one per cent, viz., 46 per cent. Consequently, it is not important to consider the reduction in variability of red blood cell volume due to its correlation with hemoglobin because keeping the number of red blood cells as a constant factor simultaneously corrects for the correlation of volume with hemoglobin.

The probable errors for partial standard deviations are obtained from the general formula:

$$\text{P.E. of } \sigma_{1.23\ldots n} = 0.6745 \frac{\sigma_{1.23\ldots n}}{\sqrt{2\,(n-1)}}.$$

The various distributions and correlation constants for both the normal male and pernicious anemia groups are listed in table 5.

The interpretation of the various factors in the normal group is as follows: 1, the standard deviations of red blood cell counts, red blood cell volume, and of hemoglobin are all reduced to about 50 per cent of their observed values if any one of the other factors is held constant; 2, there is a high degree of relationship between any two of these variables, 0.8212 to 0.8813; 3, holding hemoglobin constant reduces the degree of relationship of red blood cell count and red blood cell volume to 0.5939; 4, holding red blood cell volume constant reduces the amount of correlation between red blood cells and hemoglobin to 0.5366; 5, holding the number of red blood cells constant changes the relation between red blood cell volume and hemoglobin to a very considerable amount, 0.8212 to 0.2382.

Apparently there is not very much correlation in normal individuals between hemoglobin and red blood cell volumes if the individuals considered have similar red blood cell counts.

The interpretation of the various factors in the pernicious anemia group is as follows: 1, the standard deviations of red blood cell counts, red blood cell volume, and of hemoglobin are reduced to a greater extent than they were in the normal individual; 2, four-fifths of the variability in red blood cell volume is eliminated if both number of red blood cells and hemoglobin are held as constant factors; 3, there is a

higher degree of correlation between any two of these variables than is present in the normal group; 4, holding hemoglobin as a constant factor there is considerably more relationship between number of red blood cells and cell volume than in the normals; 5, holding number of red blood cell counts as constant there is still a correlation of 0.7612 between red blood cell volume and hemoglobin; 6, the astonishing change in the pernicious anemia group comes when red blood cell volume is held constant resulting in a negative correlation of -0.152 between number of red blood cells and hemoglobin. This would indicate that amount of hemoglobin and volume of red blood cells is the important consideration in pernicious anemia and that number of red blood cells has very little to do with the changes present. Apparently the problem to be studied in pernicious anemia is more a matter of hemoglobin production or destruction than it is red blood cell quantity.

The blood differences between the group of 40 normal men and 20 pernicious anemia patients are also listed in table 5. The differences between the means of red blood cell counts, red blood cell volume and hemoglobin are all greater than any which could arise by sampling. Likewise the zero order standard deviations of the pernicious anemia group are all significantly larger than those of the normal men. All of the partial standard deviations are significantly greater in the pernicious anemia group except $\sigma_{1.2}$, $\sigma_{2.3}$ and $\sigma_{2.13}$. The correlations of red blood cell count and volume, and of red blood volume and hemoglobin are significantly larger in the pernicious anemia patients. The correlation of red blood cell count and hemoglobin with red blood cell volume held constant is negative in pernicious anemia and differs from the normal more than would be possible by sampling. In other words, if cell volume is kept constant larger numbers of red blood cells go with greater amounts of hemoglobin in normal people, while under a similar condition in pernicious anemia larger numbers of red blood cells signify a decreased amount of hemoglobin.

In conclusion these differences between normals and pernicious anemias show that all three factors have a greater range of variation and a higher degree of inter-correlation in the latter group. It apparently indicates that physiological experimental research in pernicious anemia should be directed at hemoglobin production or destruction.

In concluding the use of this analytical example based on the variables, red blood cell counts, volume and hemoglobin, the author specifically states that the example is used herein to show the possibilities of this

type of statistical approach to quantitative physiological problems and not to draw inferences concerning pernicious anemia. The customary analysis by means of ratios and averages is woefully inadequate for descriptive purposes and does not permit the use of simple reliability tests.

There are justifiable general criticisms which might be directed against any conclusions based on these data, chief of which are non-homogeneity of the groups involved and the sparsity of cases in the pernicious anemia group, reflected in the large probable errors of various constants.

4. The use of range or arbitrary limits as a measure of normal variation. Range is frequently used by the physiologist and physician as a measure of variation. It is not an efficient statistic for this purpose since it depends upon only two observations and, consequently, has a large sampling variation.

Range is the simplest measure of spread in a frequency distribution. If the distribution is a normal one, range is related to standard deviation. The form of this functional relationship has been pointed out by E. S. Pearson (434), and Tippett (609).

To illustrate the use of range consider the following standards for blood chemistry cited by Myers (383, p. 16);

	UREA N	SUGAR	CO_2 COMBINING POWER	CREATININE	URIC ACID	NON-PROTEIN N	CHOLESTEROL	CHLORIDES AS NaCl
	mgm. to 100 cc.	*per cent*	*cc. to 100 cc.*	*mgm. to 100 cc.*	*mgm. to 100 cc.*	*mgm. to 100 cc.*	*per cent*	*per cent*
Normal.....	12–15	0.09–0.12	50–75	1–2	2–3	25–35	0.14–0.17	0.45–0.50
Beginning pathologic.....	20	0.15	−45	3.5	4	35	0.19	0.52

These standards are submitted without mentioning the numbers upon which they are based, and without discussion of factors such as sex, age, diet, etc., which might cause them to be non-homogeneous.

Gettler and Baker (207) have published one of the sets of data upon which these standards are formed. With reference to their data let us see exactly what is the significance of the standard values. The items selected for illustration are uric acid and CO_2 combining power in plasma. Gettler and Baker examined the bloods of 30 normal people, 7 females and 23 males.

The distribution constants for CO_2 and uric acid were computed and are given as follows:

		NUMBER OF CASES	MEAN ± P.E.$_M$	STANDARD DEVIATION ± P.E.
CO_2	Males	23	63.7521±0.6547	4.553 ±0.4629
	Females	7	61.1714±1.1422	4.148 ±0.8077
	Both sexes	30	63.15 ±0.575	4.593 ±0.4068
Uric acid	Males	23	2.4261±0.1347	0.9367±0.0952
	Females	7	1.000 ±0.1333	0.4840±0.0942
	Both sexes	30	2.093 ±0.1308	1.0447±0.0925

The differences between the males and females are:

(CO_2) $= 2.5807 \pm 1.3989 \therefore \frac{\bar{x}}{\sigma} = 1.84$ and the Percentage Probability = 6.6

(Uric acid) $= 1.4261 \pm 0.1632 \therefore \frac{\bar{x}}{\sigma} = 8.7$ and the Percentage Probability is zero

Although there is every indication from these data that the sexes are quite different, they are considered as homogeneous in order to evaluate range as a standard under those conditions most favorable to it.

Since the mean and standard deviations of the distributions are known, it is comparatively easy to calculate what per cent of the normal distribution lies beyond any arbitrary limit. Let $\bar{x}$ denote the deviation from the mean. If the limit of normal in CO_2 combining power is considered to be 50 for both sexes then $\bar{x}$ is the mean 63.15 minus 50, viz., 13.15. The per cent of the normal area less than the limit 50 is the area beyond the boundary line in the normal distribution of $\frac{\bar{x}}{\sigma}$, i.e., $\frac{13.15}{4.593}$ or 2.86. This area is 0.2 per cent of the total area of the distribution.[5]

Myers gives the limit of "beginning pathologic" as 45 per cent CO_2 combining power. The number of normal individuals which would occur below this limit proves to be 0.004 per cent of the normal area, i.e., 4 individuals in 10,000 normals.

[5] The table of the probability integral given on page 341, denotes the area beyond both plus and minus limits of $\frac{\bar{x}}{\sigma}$ and, therefore, must be divided by 2 in order to give the area which is less than $\frac{\bar{x}}{\sigma}$.

If the uric acid standard is considered, 19.2 per cent of normal people have more than 3 mgm. of uric acid to 100 cc.; and 3.4 per cent have more than 4 mgm. to 100 cc.

Obviously interpretation by the limits of range in relation to CO_2 combining power is far more strict than the limits of range relative to uric acid.

Another element must be investigated before the normal limits can be considered adequate; that is, how well has the mean and standard deviation been established on a sample of only 30 individuals? The probable error of the CO_2 standard deviation 4.593 is 0.4068. In other words it would not be unlikely that in so small a sample the investigator might have obtained a standard deviation smaller or larger than the one which he chose from the universe of corresponding facts. Suppose he had happened to have sampled a very small standard deviation from the universe and that the true standard deviation was larger than his observed one by the amount of one to three probable errors of the observed standard deviation. The likelihood of his having obtained an observed standard deviation + 3 P. $E._{\sigma}$ smaller than the true standard deviation of the universe would be extremely unusual. Consequently, if he judges the arbitrary limits of 50 CO_2 and 45 CO_2 combining power in light of the greatest variation which he is likely to encounter, he can feel assured that he is acquainted with the most unfavorable situation which it would be likely for him to meet.

Tables 6 and 7 demonstrate these relations for CO_2 combining power and uric acid content in milligrams to 100 cc.

When only 30 observations have been made, as in the present instance, the constants are not very well determined and their sampling errors should be considered in evaluating normal limits. If the standard deviation and mean had been formed from only 5 observations their probable errors would be large and the investigator would find it hazardous to risk his judgment as to what constituted normal or abnormal. If the standard deviation and mean had been computed from an experience of 1000, their probable errors would have been very small and he would be able to form an opinion as to the value of his limits without consideration of the sampling variation of his constants.

To summarize, physiological standards for normal variation if expressed in terms of limits should give some concept of what proportion of normal cases will be expected to fall without the limits. Furthermore, the number of cases upon which the standard is based should be sufficiently large to eliminate variation in the interpretation of the

TABLE 6

NUMBER OF CASES	MEAN ± P.E.$_m$	STANDARD DEVIATION ± P.E.$_\sigma$	LIMIT OF 50 PER CENT CO_2 AS NORMAL						LIMIT OF 45 PER CENT CO_2 AS NORMAL					
			$\bar{x}/\sigma$		$\bar{x}/\sigma + 1$ P.E.$_\sigma$		$\bar{x}/\sigma + 3$ P.E.$_\sigma$		$\bar{x}/\sigma$		$\bar{x}/\sigma + 1$ P.E.$_\sigma$		$\bar{x}/\sigma + 3$ P.E.$_\sigma$	
			Quantity	Per cent probability of smaller deviations	Quantity	Per cent probability of smaller deviations	Quantity	Per cent probability of smaller deviations	Quantity	Per cent probability of smaller deviations	Quantity	Per cent probability of smaller deviations	Quantity	Per cent probability of smaller deviations
5	63.15±1.549	4.593±1.095	$\frac{13.15}{4.593} = 2.86$	0.2	$\frac{13.15}{5.688} = 2.31$	1.0	$\frac{13.15}{7.878} = 1.67$	4.7	$\frac{18.15}{4.593} = 3.95$	0.004	$\frac{18.15}{5.688} = 3.19$	0.071	$\frac{18.15}{7.878} = 2.30$	1.1
30	63.15±0.575	4.593±0.4068	$\frac{13.15}{4.593} = 2.86$	0.2	$\frac{13.15}{4.9998} = 2.63$	0.4	$\frac{13.15}{5.8134} = 2.26$	1.2	$\frac{18.15}{4.593} = 3.95$	0.004	$\frac{18.15}{4.9998} = 3.63$	0.014	$\frac{18.15}{5.8134} = 3.12$	0.090
1,000	63.15±0.098	4.593±0.0693	$\frac{13.15}{4.593} = 2.86$	0.2	$\frac{13.15}{4.6623} = 2.82$	0.2	$\frac{13.15}{4.8009} = 2.74$	0.3	$\frac{18.15}{4.593} = 3.95$	0.004	$\frac{18.15}{4.6623} = 3.89$	0.005	$\frac{18.15}{4.8009} = 3.78$	0.008

TABLE 7

NUMBER OF CASES	MEAN ± P.E.$_m$	STANDARD DEVIATION ± P.E.$_\sigma$	UPPER LIMIT OF NORMAL URIC ACID 3 MGM. TO 100 CC.						UPPER LIMIT OF NORMAL URIC ACID 4 MGM. TO 100 CC.					
			$\bar{x}/\sigma$		$\bar{x}/\sigma + 1$ P.E.$_\sigma$		$\bar{x}/\sigma + 3$ P.E.$_\sigma$		$\bar{x}/\sigma$		$\bar{x}/\sigma + 1$ P.E.$_\sigma$		$\bar{x}/\sigma + 3$ P.E.$_\sigma$	
			Quantity	Per cent probability of larger deviations	Quantity	Per cent probability of larger deviations	Quantity	Per cent probability of larger deviations	Quantity	Per cent probability of larger deviations	Quantity	Per cent probability of larger deviations	Quantity	Per cent probability of larger deviations
5	2.093±0.3523	1.0447±0.2491	$\frac{0.907}{1.0447} = 0.87$	19.2	$\frac{0.907}{1.2938} = 0.70$	24.2	$\frac{0.907}{1.792} = 0.51$	30.5	$\frac{1.907}{1.0447} = 1.83$	3.4	$\frac{1.907}{1.2938} = 1.47$	7.1	$\frac{1.907}{1.792} = 1.06$	14.5
30	2.093±0.1308	1.0447±0.0925	$\frac{0.907}{1.0447} = 0.87$	19.2	$\frac{0.907}{1.1372} = 0.80$	21.2	$\frac{0.907}{1.3222} = 0.69$	24.5	$\frac{1.907}{1.0447} = 1.83$	3.4	$\frac{1.907}{1.1372} = 1.68$	4.7	$\frac{1.907}{1.3222} = 1.44$	7.5
1,000	2.093±0.0223	1.0447±0.0158	$\frac{0.907}{1.0447} = 0.87$	19.2	$\frac{0.907}{1.0605} = 0.86$	19.5	$\frac{0.907}{1.0921} = 0.83$	20.3	$\frac{1.907}{1.0447} = 1.83$	3.4	$\frac{1.907}{1.0605} = 1.80$	3.6	$\frac{1.907}{1.0921} = 1.75$	4.0

status of questionable cases. Range is an inefficient statistic for these purposes and should be discarded.

5. The rejection of atypical observations. The best practical solution for the very disturbing problem of how and when to reject widely divergent cases arises from the consideration of distribution limits discussed in the previous section.

There are a number of good expositions by various authors upon this subject none of which, however, solves the question. Brunt (75, p. 129) states the problem as follows:

> An observer making a series of observations of any kind has power to reject any observation if he is certain that it is vitiated by some unusual sources of error which do not affect the other observation in the series. To put this in other words, the observer is to a certain extent free to choose the time for making his observations so that the external conditions shall vary as little as possible during the series. He is supreme in his own department, having the power to retain or reject observations according to his judgment of the extent to which the external causes of error react upon his measurements.
>
> But when the observational material is put into the hands of the computer there arises a new question. Shall the computer be allowed to reject any observation whose residual is much larger than those of the remaining observations? He should clearly be allowed to reject an observation when he is convinced that it is affected by an error from some unusual source, which does not affect the other observations in the series; or if the observation is clearly spoiled by some definite blunder, such as the mis-reading of a scale by five divisions. It is sometimes possible to correct blunders of this type, and to retain the observation, but the greatest caution is necessary in making such corrections. The real difficulty lies in deciding whether a large residual is due to some unusual source of error, or is due to the chance occurrence of a large number of small accidental errors with the same sign. If the latter alternative be true, the large residual is in accordance with the law of error, and its rejection will decrease rather than increase the accuracy of the final result.
>
> A number of criteria, based on more or less rigid analysis, have been put forward by various writers. The best known of these is Peirce's Criterion. The underlying principle is that the doubtful observations should be rejected when the probability of the system of errors obtained by retaining them is less than the product of the probability of the system of errors obtained by rejecting them, multiplied by the probability of making so many, and no more, abnormal observations. As this criterion is not in general use, and is rather tedious in its application, we shall not enter into the full proof. The reader who desires to know more of it is referred to Chauvenet's *Theoretical and Practical Astronomy*, Vol. II, Appendix, §58, where Peirce's proof is reproduced almost word for word; and to the proof and tables by Gould in *Astronomical Journal*, Vol. IV, and *U. S. Coast Geodetic Survey Report*, 1854, pp. 131, 132.

The general consensus of opinion of statisticians with reference to the goodness of these criteria is quite variable. The simplest approach

to a practical solution is to compute the theoretical chances which exist and see how divergent the observed experience is from the theoretical. For instance, in the previous example, table 6, it would be surprising if there were not approximately two normal individuals out of a thousand who had a CO_2 combining power below 50 cc. per 100. To obtain the limit beyond which one might reasonably expect that not even a fraction of one case in a thousand (for example $\frac{1}{2}$ of one case) would deviate by sampling is obtained as follows: $\frac{\bar{x}}{\sigma}$ must equal a probability of 0.0005 or less, in order to represent $\frac{1}{2}$ of one case in a thousand. Consequently, from a normal probability table it is seen that $\frac{\bar{x}}{\sigma}$ must not be less than 3.29 to be equivalent to such a probability. To be on the safe side take as the σ, value of $\sigma + 3$ P.E.$_\sigma$, or in other words a standard deviation so large that it would arise only once in 50 times by sampling.

Then,

$$\frac{\bar{x}}{\sigma + 3 \text{ P.E.}_\sigma} = \frac{\bar{x}}{5.8134} = 3.29$$

$$\bar{x} \text{ (deviation from mean)} = 3.29\ (5.8134) = 19.126$$

The required limit is:

$$\text{Mean} - \bar{x} = 63.15 - 19.126 = 44.024$$

A rejection of an individual beyond the limit 44 CO_2 combining power would mean that only 5 times in ten thousand would a normal individual have such a CO_2 value or less.

If the divergent observation is discarded it should always be published as an unexplained deviation.

6. Estimation of the reliability of proportions. There are a great many medical and physiological problems which do not involve measurable quantities. For instance, such facts as the following: symptoms classified as present or not present; findings, negative or positive; experiments, successful or unsuccessful, etc. In all such situations, the data are considered to be qualitative. Data of these types become quantitative if numbers of individuals are classified into such mutually exclusive categories.

Statistical analyses, directed at these types of data, represent the simplest distributions which can be treated by statistical methods. For illustration, assume that cases of gall-bladder disease are classified

into those which are jaundiced and those not jaundiced. A distribution of degree of jaundice is assumed. If jaundice could be measured by some scale, as for instance amount of bile pigment in the blood, a better description of the symptom could be obtained. Since only one point on the scale is available, all cases must be thrown into either the jaundiced or non-jaundiced groups.

In order to draw inferences concerning the degree of goodness with which this actually observed proportion of jaundiced cases has been selected out of an infinite population of such samples, the hypothetical distribution of such proportions is assumed to be fitted by a normal or Gaussian curve. In other words, if the investigator has computed the probability of jaundice occurring in many samples of 25 patients, he can then compute the standard deviation of his entire set of proportions. If the standard deviation which he obtained in this manner were the same as that arising from a corresponding normal distribution, it would be said to correspond to the standard deviation expected by sampling; if it were a larger standard deviation than that of the normal curve, the conclusion would be that some other factor than sampling variation was influencing the proportion of jaundice cases.

As seen in figure 2a, the normal distribution is symmetrical; consequently, the probability, p, of an event happening which is larger than the mean, is half of the total area under the normal curve. If the total area is considered to be unity, the $p = 0.5$. The probability of the event not happening, q, is the total area minus 0.5, i.e., $1 - p = q = 0.5$.

If the total area is assumed to be computed from a frequency (n) of 25 individuals, the average is

$$n(p) = (25)\ 0.5 = 12.5$$

Assume that a hypothetical distribution of p values has been computed. These values will distribute themselves according to a normal curve, the standard deviation of which is given by the expression

$$\sigma = \sqrt{\frac{(p) \text{ times } (q)}{n}}$$

In this instance the

$$\sigma = \sqrt{\frac{(0.5)\ (0.5)}{25}} = \sqrt{\frac{0.25}{25}} = \sqrt{0.01} = 0.1$$

The standard deviation of the proportion 0.5, is equal to 0.1.

This signifies that if the hypothetical infinite distribution were normal and the size of sample computed each time was 25, the true value of p existing in the universe from which the samples were drawn would be expected to fall within the boundaries of 0.5 $\pm$0.1, i.e., between 0.4 and 0.6 in 68.26 per cent of the times (fig. 2e).

Assuming a distribution of np, or average values in samples each 25 in number, the standard deviation of the means is found by the equation σ of the mean (also termed the expected number) =

$$\sqrt{(p) \text{ times } q \text{ times } n} = \sqrt{(0.5)\ (0.5)\ 25} = \sqrt{6.25} = 2.5.$$

In other words, it is reasonable to expect that if the hypothetical infinite universe is normal, and the size of the sample 25, the true average would fall 68.26 per cent of the time between the limits of 12.5 $\pm$ 2.5, that is, within the boundaries of 10 and 15.

The proof and derivation of these useful equations are given by many authors (see cross-index to bibliography under mean).

The proportion of observed items will rarely give values of p exactly equal to 0.5; consequently it is necessary to know how much the formula for σ deviates in the accuracy with which it describes the distribution of proportions as p becomes relatively larger or smaller. The equations as given above are accurate and can be applied to obtaining the standard deviations due to sampling of any proportion p or any average np, no matter how small p might become, *if* the frequency n be sufficient in size to adequately establish the average np. In other words, the value of p should be well determined relative to the size of n. For instance, if p is 0.1 and the sample 20, np would be established with about the same degree of relative accuracy as an average upon 2 cases with a p of 0.5. If the p were 0.0005 and 100,000 observations were involved, np would be established with about the same relative degree of goodness as a mean computed on 50 cases with a p of 0.5.

In order to illustrate the application of these equations, let us consider the distribution of red blood cells previously noted on page 280. Assume that one could only measure red blood cell counts which fall above or below the count of 5.4 millions.

Then

n = size of sample = 40
Number above 5.4 millions = 5
Number below 5.4 millions = 35
$p = 5/40 = 0.125$
$q = 1 - p = 35/40 = 1 - 0.125 = 0.875$

In a hypothetical normal distribution of such proportions drawn from an infiinite universe

The average $= np = 5$

The σ expected number $= \sqrt{npq} = \sqrt{40\ (0.125)\ (0.875)} = 2.0917$

The σ of $p = \sqrt{\frac{pq}{n}} = \sqrt{\frac{(0.125)\ (0.875)}{40}} = 0.0529$

From these calculations the investigator could expect that the true proportion of red blood cells existing in the universe from which his sample was drawn would lie within the value of 0.125 ± 0.0529, 68 per cent of the time.

7. Estimation of the significance in differences between proportions. The principal application of the standard deviation of a proportion comes from its value in determining the degree of significance between the proportions of two samples. If the two samples are indicated as 1 and 2, and $p_1 \pm \sigma$ of p_1 and $p_2 \pm \sigma$ of p_2 are known, then the difference between the proportions p_1-p_2, can be interpreted in light of the standard error of the difference, i.e.,

$$\sigma_{\text{diff.}} = \sqrt{(\sigma_1)^2 + (\sigma_2)^2}$$

An excellent example in the practical use of this equation is given in a paper by A. S. Parkes, on "The effects on Fertility and the Sex-Ratio of Sub-Sterility Exposures to X-Rays" (400). Parkes established the per cent of normal males in total births:

Males = 379, Females = 356
Per cent Males = 51.56 or a p_{normal} (in terms of unity) of 0.5156

The standard deviation of this proportion expected by sampling

$$\sigma_{\text{normal}} = \sqrt{\frac{(0.5156)\ (0.4844)}{735}} = 0.01843$$

In a similar manner the proportion of males in his combined series 0–4 days after x-ray treatment

$$P_{(0\text{–}4)} = 0.594 \pm 0.0426$$

and the proportion 5–18 days after x-ray treatment

$$P_{(5\text{–}18)} = 0.336 \pm 0.0394$$

The differences between $P_{(0\text{-}4)}$ and $P_{\text{normal}} = +0.078 \pm 0.0464 = 1.68$. This value of $\frac{\bar{x}}{\sigma}$ signifies that in only 9 times out of 100 could one expect to get such a difference by the sampling process. The difference between $P_{(5\text{-}18)}$ and P_{normal} is $-0.180 \pm 0.0435 = 4.14$. Such a difference would occur only 4 times in 100,000 by sampling. Therefore, Parkes was justified in concluding with reference to the time period 5–18 that the difference in per cent of male births must be a real difference, i.e., one which could not be produced by sampling, and probably was due to the x-ray treatment.

In many situations, the investigator is not particularly interested in the ratios, but merely wishes to know if the samples differ from each other more than can be expected by sampling. Such questions can be most readily answered by computing the Chi-square value (χ^2) for a four-fold table. In this example of Parkes, for instance, the data could have been given as follows:

	MALES	FEMALES	TOTAL
Normal	379 (a)	356 (b)	735 ($a + b$)
Combined series, 0–4 days after x-ray	79 (c)	54 (d)	133 ($c + d$)
Total	458 ($a + c$)	410 ($b + d$)	868 ($a + b + c + d$)

Algebraically χ^2 for a four-fold table is computed as follows:

$$\chi^2 = \frac{(ad - bc)^2 (a + b + c + d)}{(a + c)(b + d)(a + b)(c + d)}$$

By substitution and solving, the χ^2 is found to be 2.773.

The probability for which χ^2 stands can be looked up directly in Yule (687, p. 385–6,) or in this paper on page 341. Since $\chi^2 = \left[\frac{\bar{x}}{\sigma}\right]^2$, the probability of $\pm \frac{\bar{x}}{\sigma} = \pm \sqrt{2.773} = \pm 1.67$, signifies that there are 9 chances in a hundred for such a difference as exists between these two groups to arise by sampling.

These two approaches have arrived at the same answer. When frequencies are low, the χ^2 method of computation is more accurate

than that of obtaining the significance of the difference between the two proportions. The two methods are numerically equal if the formula

$$\sigma = \sqrt{\frac{pq}{n}}$$

is determined by using the p and q in each instance which come from the total experience; i.e.,

$$p = \frac{458}{868} = 0.5276$$

and

$$q = 1 - p = \frac{410}{868} = 0.4724$$

Another example of the use of χ^2 is cited to show the usefulness of this tool in drawing inferences. P. Heinbecker and E. I. Irvine-Jones (269), in a paper on the "Susceptibility of the Eskimos to the common cold and a study of their natural immunity to diphtheria, scarlet fever and bacterial filtrates," give the following data on the relation of skin reactions to staphylococcus filtrates (aureus)

	NEGATIVE	POSITIVE	TOTAL	PER CENT POSITIVE
Eskimos	12	36	48	75.0
Control group	2	27	29	93.1
Total	14	63	77	

The χ^2 value, 3.98, tells us that the difference between 93.1 and 75.0 per cent (that is, 18.1 per cent) could arise only 5 times in a hundred by sampling. Therefore, it is probable that the difference 18.1 per cent is a real difference, although the authors conclude that "the results from a staphylococcus aureus strain were not unlike those of the American Controls although the Eskimos were rather less susceptible."

8. Estimation of the number of observations necessary in order to prove that a difference is significant to any specified degree of probability. The proportions of per cents of positive cases in the Eskimos and control groups are not formed on very many observations. Consequently, Heinbecker and Irvine-Jones would be justified in answering the Chi-square solution of the problem by saying "Yes, the chances do seem to be in favor of this difference being a real one, but in view of the small

numbers, we wish to have these chances more overwhelmingly in our favor." Such a retort would raise the question,—approximately how many observations would be necessary to show that this difference is significant to any specified degree of probability?

The difference ($\bar{x}$) between the Eskimos and controls is 18.1 per cent. In the sample this difference, in view of its standard error, i.e., $\pm \frac{\bar{x}}{\sigma_{\text{diff.}}} = \frac{18.1}{9.07} = 1.9956$, demarcates the limit beyond which is approximately 5 per cent of the area under a normal curve. Assume that the authors wished to establish this difference to a degree of surety one in a hundred. Then the area under the normal curve (see p. 341), beyond plus and minus limits of $\frac{\bar{x}}{\sigma}$, must equal 0.01. The value $\frac{\bar{x}}{\sigma_{\text{diff.}}}$ which brings about this desired result would be 2.58. Since $\bar{x}$ is constant, viz., a difference of 0.181 (in terms of unity) the change must occur in the σ of the difference.

$$\text{The } \sigma_{\text{difference}} = \sqrt{(\sigma_e)^2 + (\sigma_c)^2}$$

when

$$\sigma_e = \sqrt{\frac{\overline{pq}}{n_e}}$$

and

$$\sigma_c = \sqrt{\frac{\overline{pq}}{n_c}}$$

Substituting these values:

$$\sigma_{\text{difference}} = \frac{0.181}{\sqrt{\frac{(pq)}{n_e} + \frac{(pq)}{n_c}}} = 2.58$$

where n_e and n_c are the unknown number of Eskimos and controls respectively. The number of Eskimos actually observed was 48; the number of controls actually observed was 29. If the ratio of $\frac{n_e}{n_c} = \frac{48}{29} = 1.66$ was maintained, then $n_e = 1.66\ n_c$. Solving in above equation, $n_e = 80.4$ and $n_c = 48.4$. This means that if there had been approxi-

mately 81 Eskimos and 49 controls, the difference 18.1 between the percentage 75 and 93.1 could have been proved significant to the surety of one chance in a hundred.

If the reliability desired was chosen as one chance in a thousand against the statement that "there is a difference between these per cents other than that due to sampling," the same type of solution yields the information that such a degree of surety could have been established if approximately 129 Eskimos and 78 controls had been examined.

If the investigators were limited to 29 controls, but unlimited as to the number of Eskimos, and if they desired to establish a degree of certainty of one in a hundred, the equation could not be solved. This indicates that regardless of how many Eskimos might be examined, the authors could never have established the difference of 18.1 per cent with the degree of certainty of one in a hundred unless more than 29 controls were available.

Application of Chi Square in physiology. The Chi Square, χ^2, value for a fourfold table is the simplest example of the general application of the Chi Square function. Fisher (190, p. 77) defines the function as follows:

> If m is the number expected, and $m + x$ the number observed in any class, we calculate
>
> $$\chi^2 = S\left(\frac{x^2}{m}\right)$$
>
> the summation extending over all the classes. This formula gives the value of χ^2, and it is clear that the more closely the observed numbers agree with those expected the smaller will χ^2 be; in order to utilize the table, it is necessary to know also the value of n, with which the table is entered. The rule for finding n is that n is equal to the number of degrees of freedom in which the observed series may differ from the hypothetical; in other words, it is equal to the number of classes the frequencies in which may be filled up arbitrarily.

The usual situation in which χ^2 will prove to be particularly valuable to the physiologist is represented when he wishes to know if different series of observations have been sampled out of the same universe of facts.

As an example to show the computation technique of χ^2, table 8 has been prepared from the data given by W. L. Culpepper in "Report on five thousand blood types using Moss's grouping" (112).

The χ^2 value of 101.4 with an n of 3 stands for a probability of zero. There is no chance for such differences as the above to arise by sampling.

Since the probability that the distributions of Culpepper and Moss were sampled from the same universe is zero, therefore, reasoning con-

TABLE 8

Example of computation of Chi Square of two observed distributions

	BLOOD GROUPS				
	I	II	III	IV	Total
(A) Moss' series.....	160 (*a*)	640	112	688	1600
(B) Culpepper's series.	259	1803	714	2224	5000
(A and B) Total.....	419	2443	826	2912	6600
$\left(\frac{\text{A values}}{1600}\right)$ % Moss...	0.10	0.40	0.07	0.43	1.00
$\left(\frac{\text{B values}}{5000}\right)$ % Culpepper..	0.0518	0.3606	0.1428	0.4448	1.00
Difference in per cents..	+0.0482	+0.0394	−0.0728	−0.0148	0.00
Squared difference.....	0.002,323,24	0.001,552,36	0.005,299,84	0.000,219,04	
$\frac{\text{Squared Diff.}}{\text{A and B values}}$.....	0.000,005,544,725	0.000,000,635,432	0.000,006,416,271	0.000,000,075,220	0 000,012,671,65

χ^2 = (Total of *A*) (Total of *B*) (0.000,012,671,65) = (1600) (5000) (0.000,012,671,65) = 101.4

The *n* to use in χ^2 Table appendix of this paper, page 341, is computed as:

n = (number of rows −1) (number of columns −1) + 1 = (4-1) (2-1) + 1 = 4

$\therefore \chi^2 = 101.4$ and p = zero

versely, it is probable that some other factor than sampling entered into the collection of the two sets of data—such as technique, race, chronological time, etc.

Culpepper also comes to this conclusion.

χ^2 can be computed according to the definition;

$$\text{Sum of } \left[\frac{(\text{Theoretical-observed})^2}{\text{Theoretical}}\right]$$

The theoretical values must be obtained for each cell of the table. For instance, the theoretical frequency for cell (a) in table 8 is obtained from the marginal values. The theoretical probability that a case will fall in Blood Group I is $\frac{419}{6000}$, the theoretical probability that it will fall in the row of Moss' data is $\frac{1600}{6600}$. If these two probabilities were independent, the relative occurrence of an individual being classified as unit (a) is $\frac{419}{6600}$ times $\frac{1600}{6600} = 0.0153903$. The theoretical number that should have occurred in cell (a) if the events were independent is $(0.0153903)\ 6600 = 102$. The unit of χ^2 which is formed by this cell is given by

$$\left[\frac{(\text{Theoretical-observed})^2}{\text{Theoretical}}\right] = \frac{(102-160)^2}{102} = \frac{(58)^2}{102} = \frac{3364}{102} = 32.98$$

Culpepper reports his 5000 cases by samples of a thousand each as follows:

	BLOOD GROUPS				
	I	II	III	IV	TOTAL
First thousand	52	360	117	471	1,000
Second thousand	50	363	135	452	1,000
Third thousand	47	352	156	445	1,000
Fourth thousand	55	365	150	430	1,000
Fifth thousand	55	363	156	426	1,000
Total	259	1,803	714	2,224	5,000

A scrutiny of these five different groups of a thousand each raises the question of homogeneity in the mind of the investigator. It is obvious that the fourth and fifth groups are very similar; also the first three seem

to be more or less alike. The first three differ to a somewhat greater amount from the last two. χ^2, computed on the entire contingency table of 5 samples, is 12.03. The number of free cells + one in the table, i.e., n, is 13 (see p. 341), and the $p = 0.44$.

The probability of obtaining 5 samples with a χ^2 as large or larger than 12.03 from a universe of blood groups is 44 in a hundred. The differences between Culpepper's five samples of 1000 each prove to be no more than those ordinarily expected by sampling.

Since examples of the use of χ^2 practically do not exist in the field of physiology, and since it can be employed with benefit in a great variety of physiological problems, another illustration has been developed from the data of S. A. Asdell on "Time of Conception and of Ovulation in Relation to the Menstrual Cycle" (17).

His problem is to evaluate the data of various authors upon sex ratio of births relative to the time of conception. Most data on this subject can be ignored, because of improper collection. Five authorities remain whose conclusions must be evaluated. Asdell gives the results of these men as follows:

Sex ratio of births relative to the time of conception

AUTHORITY	1-9 DAYS		10-14 DAYS		15-23 DAYS		TOTAL	
	Male	Female	Male	Female	Male	Female	Male	Female
Siegel	37	7	4	9	3	20	44	36
Nurnberger	41	39	29	27	26	21	96	87
Jaeger	32	16	8	14	12	17	52	47
Data from Hecker and Buhl, and Schlichting	93	82	46	48	63	58	202	188
Furst	40	18	23	28	28	35	91	81

The practical questions asked and the statistical χ^2 answers are as follows:

1. Disregarding time of cycle, does the proportion of males differ among the various authors?

   Answer: χ^2 on males and females in total column for all five authors is equivalent to a probability of practically unity; therefore, the per cents of males collected by various authors do not differ.

2. In the group determined on the 10–14 days of cycle, does the proportion of males differ among the various authors?

Answer: χ^2 shows that by sampling alone, 56 out of 100 times there would have been a divergence between these authors as large as that which actually exists; therefore, the per cents of males observed by various authors in this period do not vary more than would be expected as a sampling difference.

3. In the group determined on the 15–23 days of cycle, does the proportion of males differ among various authors?

   Answer: χ^2 shows that by sampling, such a divergence would occur, only once in a hundred times; therefore, the per cents of males observed by the five authors do vary more than would be anticipated as a sampling difference. Moreover, it indicates that Siegel is responsible for most of this divergence.

4. In the group between 15–23 days of cycle, does the proportion of males differ among various authors omitting the experience of Siegel?

   Answer: χ^2 indicates the sampling probability to be 57 in 100; consequently, Siegel's data in this time period seem to be the only disturbing factor.

5. How widely do Siegel's data in this 15–23 day period deviate from the sum total of all the experience of other authors?

   Answer: χ^2 indicates that the sampling probability is only a tenth of one per cent: there is no doubt that extraneous factors besides sampling enter into Siegel's data of this cycle period which do not affect the material of other authors.

6. In the group based on the first 9 days of the cycle, does the proportion of males vary with different authors?

   Answer: The possibility of sampling such a difference, as determined by χ^2, is 7 in 10,000; therefore, the per cents of males observed by various authors in this period vary more than would occur by simple sampling. Once again Siegel's data are the most divergent.

7. In the group, 1–9 days of the cycle, does the proportion of males vary between the other authors, omitting Siegel?

   Answer: The sampling probability is 7 per cent. Furst now seems to be the disturbing element in causing this relatively large deviation from the expected.

8. In the group 1–9 days of the cycle, does the proportion of males vary between the authors Nurnberger, Jaeger and the data from Hecker, Buhl and Schlichting?

   Answer: The probability of such deviations arising by sampling

is 19 in 100; therefore it is not very likely that such a variation between the per cents of males is more than that which would arise by simple sampling.

9. Do the results of Furst in these first 9 days differ from the sum total results of Nurnberger, Jaeger, Hecker, Buhl and Schlichting?

   Answer: The probability of such a sampling difference as shown by χ^2 is only 5 in 100; therefore the per cents of males in Furst's data can be considered to vary significantly from the others.

10. How widely do Siegel's data in this period deviate from the sum total experience of the other authors with reference to per cent of males?

    Answer: χ^2 shows the possibility of sampling differences so large to be only 6 in 10,000; therefore the per cent of males obtained by Siegel varies from the other authors more than would be anticipated by sampling.

11. Since both Siegel and Furst have larger proportions of males in the first 9 days of the cycle than do the other authors, the question arises: Do they differ from each other?

    Answer: χ^2 gives a sampling possibility of only 8 in 100; therefore Siegel has a higher per cent of males than Furst and this difference is probably due to some factor other than simple sampling.

To summarize, χ^2 has rendered a solution for the difficult problem of telling which of these authors are likely to be dealing with homogeneous experience. All authors agree with respect to the per cent of males in the period 10–14 days of the menstrual cycle. Siegel has a significantly higher proportion of females than the remaining authors in the 15–23 day period. Both Siegel and Furst differ significantly from the other authors in having higher proportions of males in the first 9 days, and Siegel has a proportion of males that is probably significantly greater than Furst in this period.

It is important to emphasize at this point that no interpretation has been made as to which of these data are the "best." χ^2 points out differences which are not sampling differences, and there it stops! Any interpretation as to which author's conclusions will be accepted must come out of a consideration of his experimental set-up. In fact, in this present example, there are strong reasons which tempt one to accept the statements of Jaeger as nearest to the truth, regardless of the fact that he differs from the other authors. However, this is a matter of personal judgment and arises from a consideration of how Jaeger obtained his data.

The χ^2 test is frequently applied as a method of estimating goodness of fit in frequency distributions. One example will suffice to show this process. The distribution of observed red blood cells, page 279, was fitted by a normal curve. The goodness with which the theoretical area of the curve approximates the observed is tested by χ^2 as follows:

RANGE	OBSERVED FREQUENCY	THEORETICAL FREQUENCY OF NORMAL CURVE	(THEORETICAL-OBSERVED)^2	$\frac{(\text{THEORETICAL-OBSERVED})^2}{\text{THEORETICAL}}$
Under 4.6	6	4.96	1.0816	0.2181
4.6–4.7	4	6.51	6.3001	0.9678
4.8–4.9	11	9.02	3.9204	0.4346
5.0–5.1	8	8.80	0.6400	0.0727
5.2–5.3	6	6.23	0.0529	0.0085
5.4 and over	5	4.49	0.2601	0.0579
Total.....	40			χ^2 = total = 1.7596 Number of cells = 6 $\therefore$p (p. 341) = 0.88

The p of 0.88 indicates that the normal equation can be considered to be a good fit of the observed frequency distribution, since by sampling alone areas as widely variable as those given by the normal curve would be drawn 88 times in 100.

C. CAUTIONS TO BE OBSERVED IN THE USE OF STATISTICAL METHOD. As indicated in the preceding section of this paper, statistical method is a tool of particular importance to the laboratory worker in physiology, for four reasons: first, it helps to describe a multiplicity of observations in simple terms; second, it assists in the establishment of reasonable limits for inferences deduced from the data; third, it makes possible the distinctions of significant and non-significant experimental differences, and fourth, it affords a measure of goodness of fit in curve fitting.

There are assumptions behind this theory of statistical method. The method itself based upon these assumptions is an ideal which can never be wrong. The difficulty comes when observed facts which do not agree with the assumptions are judged by inferences which arise from the ideal situation. If every assumption made by the statistical theory had to be rigorously applied to observed data before using the statistical method, there would be extremely few situations in which general inferences could be made by its use.

For practical purposes there are comparatively few faults in the application of statistics which lead one into gross errors of judgment.

The principal admonitions are grouped into 12 categories. There are minor limitations which do not need to be considered.

1. Do not analyze frequency distributions whose elements are not independent. In physiology experimental groups whose elements are not independent are frequently considered to be homogeneous. For the most part this fault occurs in two kinds of problems; first, in those which are concerned with numbers of observations upon the same individual and summate such data with corresponding facts about different individuals, and second, in those which involve hereditarial facts about families which are considered to be identical in value to corresponding facts about race. In both of these situations the elements are not independent. Variation in measurements on the same individual, even though such variation be large, is not as great as if a series of different individuals be measured. Likewise in heredity studies, variations within the family always are less than those within the race.

2. Fix no arbitrary standard of probability as an indication of significance. It has become a standard statistical practice to take the boundary lines of plus and minus 3 probable errors (fig. 3d), or plus and minus 2 standard deviations (fig. 2f) which represent approximately 5 chances in 100, as being those boundary lines which separate significance and non-significance. This is a very arbitrary concept and should not be permitted to warp physiological judgments. The boundary line of significance should be determined by the individual experimenter with reference to his particular problem. For instance, suppose he were interested in establishing the dosage of a lethal drug, he would not wish to come within one chance in a million of giving a lethal dose to a patient due to the sampling variation in drug effect. However, if he were gambling on a horse at the race track he might be only too glad to have a chance of 60 to 40 in his favor. It is rather astonishing to say the least that so many investigators are willing to evaluate their scientific opinions at 5 in a hundred.

3. Do not make the statement that no difference exists because no significant difference can be demonstrated. One must remember that the mean of sampling differences is distributed about a 50 per cent chance (fig. 2a). On the other hand, the mean differences between two samples is a zero difference (p. 294). As deviations in differences between samples progress below 50 per cent towards zero, sampling variations become less likely because the samples are becoming more and more different; as deviations progress from 50 per cent towards 100 per cent the sampling variations become less likely because the samples are

becoming identical. One is just as likely to get a deviation by sampling which is 0.001 as a sample of 0.999. In other words, it is not likely that one can get samples too nearly alike. This concept has been made use of occasionally to detect fraudulent data, because such data are almost always distributed too nearly to theoretical values to have arisen as a sampling deviation. The investigator is prone to assert that because a difference "is not significant, there is no difference." If he desires a boundary line which establishes 99 chances in favor of a real difference to one in favor of no difference before he claims to have a significant difference then, to be consistent, he should demand 99

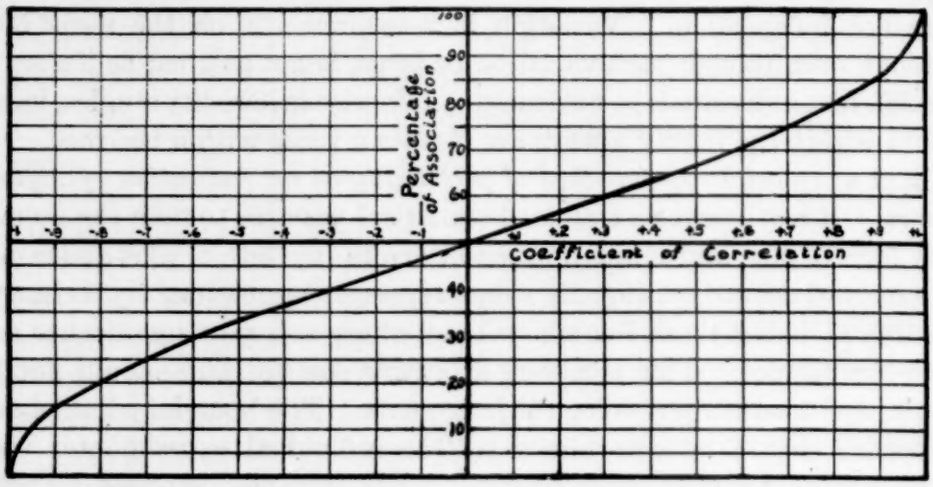


Fig. 4. Showing the relation between the correlation coefficient and the "per cent" association.

chances in favor of no difference to one in favor of a real difference before he states that the samples are identical.

4. Do not use the correlation coefficient in bivariant data which are non-linear. One of the assumptions from which the correlation coefficient is developed states that the means of one variable for particular values of the other must be approximately linear. There is some leeway in the literal application of this assumption. Probably the easiest way by which to test linearity is to make a careful spot diagram and form a visual judgment. Most physiological correlations are linear in type. Non-linearity is customarily observed in growth problems providing the time period ranges over 10 to 15 years. A constant, eta (η), can be computed from the correlation table by means of which it is possible to test the data for non-linearity. For practical purposes the constant η

does not need to be computed if care be taken to judge linearity from spot diagrams. In case such visualization indicates that the material might be curvilinear, a test of linearity should be made before the correlation coefficient is interpreted.

5. Do not interpret the scale of the correlation coefficient as a percentage scale. Among practical statistical workers, the scale of a correlation coefficient which goes from +1 (perfect positive correlation), to 0 (no correlation) and then to −1 (perfect negative correlation), is frequently interpreted to signify proportionate changes in degree of relationship. This is not true. Zero correlation is the situation in which there is no relation between the variables. For instance, in the fourfold table it is quite obvious that the four cells are in equal balance.

	A	B	Total
C	50	50	100
D	50	50	100
Total	100	100	200

The χ^2 is zero indicating a p of unity. Therefore, this kind of a division represents zero correlation and the balance of 50 per cent exists in each of the marginal totals.

The entire range of relations between various values of the correlation coefficient is given in terms of percentage by the diagram (fig. 4) which was made by Miss Parker, (398). From this figure it is seen that a correlation of +0.6, which workers are accustomed to consider rather high, stands for a shift in the relative degree of relationship of only 20 per cent. A change from a correlation coefficient of 0 to 0.1 is relatively equivalent to the change between a correlation of 0.9 to 0.93.

6. Do not confuse degree of relationship with cause and effect. Correlation of any degree merely indicates that a relation exists between certain variables. This relation might or might not be causal in character.

The allocation of cause comes through experimentation. The function of correlation is to point out the factors upon which it is worth while to experiment.

7. Be sure there is no correlation between errors in the application of difference formula. The complete formula for probable error of a difference between two functions is given by the equation:

$$\text{P.E. of difference} = \sqrt{(\text{P.E.}_1)^2 + (\text{P.E.}_2)^2 - 2\, r_{12}\, \text{P.E.}_1\, \text{P.E.}_2}$$

in which subscripts 1 and 2 represent the two variables involved and r the correlation between errors. In the great mass of physiological problems where this equation is used, the correlation coefficient between the errors can be assumed to be zero. However, experiments can be obtained in which r_{12} might not be zero. For instance, suppose that one was testing the first and second samples of CO_2 taken from a Haldane respiratory bag. If one should compute the mean of the CO_2 in a series of first samples and another in a series of second samples and then desire to know if the difference between these means were significant in light of the probable error of the difference, the correlation between sampling errors would necessarily enter into consideration. This is due to the fact that the total amount of CO_2 remaining in the bag would be changed slightly due to the removal of the first sample. Fortunately such instances are few in number and are usually trivial in character. They can be located by examining the experimental procedure in the problem.

8. Do not confuse per cent of quantity with probability. Probability statements are very frequently confused with percentage statements which do not indicate probability.

For example, the limits of normal basal metabolism are usually defined as plus and minus 10 per cent. Within these limits, which essentially stand for quantity in terms of calories per square meter per hour, occur about 95 per cent of normal adults. In statistical terms, therefore, these limits demarcate a frequency zone of approximately plus and minus two standard deviations. However, many situations might shift the boundaries of plus and minus 10 per cent in basal metabolism rates, with respect to their significance in terms of frequency. For instance, in childhood, individual variation is higher and consequently the limits of plus and minus 10 per cent include only about 90 per cent of normal children.

9. Be sure to describe relations of variables before computing ratios or indices. The physiological literature is full of analyses of data by ratios such as color index, volume index, saturation index, nutrition indices, anthropological indices, repiratory quotient, etc.

Critical use of such indices necessitates that the variables constitut-

ing the index be adequately described. In no other way is it possible to know whether the mathematical function assumed by the form of the index is reasonable for the data involved. After the index is applied to the data, all opportunity to obtain such a description is lost.

10. Never use Chi Square, χ^2, except upon frequency observations. The theory of χ^2 is developed upon the assumption that frequencies have been sampled. To shift frequencies to a percentage basis results in erroneous conclusions. To compute χ^2 on measured quantities is also incorrect. If measured quantities have been counted and frequencies of the counts are being compared, then χ^2 can be used.

11. Never try to explain why differences occur by any method designed purely to test the significance of differences. Tests of significance are always directed at the problem of telling *how* differently two or more samples deviate from each other or *how* widely statistics might diverge without deviating beyond sampling possibilities. The question of *whether* differences are significant can be answered by statistics, that of *why* they are different is beyond the scope of any tests of significance.

12. Do not abuse the application of the probable error concept. This caution is well expressed by Yule (687, p. 281).

> The student must, therefore, be very careful to remember that even if some observed difference exceeds the limits of fluctuation in simple sampling, it does not follow that it exceeds the limits of fluctuation due to what the practical man would regard—and quite rightly regard—as the chances of sampling. Further he must remember that if the standard error be small, it by no means follows that the result is necessarily trustworthy: the smallness of the standard error only indicates that it is not *untrustworthy owing to the magnitude of fluctuations of simple sampling.* It may be quite untrustworthy for other reasons: owing to bias in taking sample, for instance, ... On the other hand, of course, it should be borne in mind that an observed proportion is not necessarily incorrect, but merely to a greater or less extent untrustworthy if the standard error be large.

It is well to remember that the term probable error is a distinct misnomer. "Probable error" is neither "probable" nor "error." In an observed distribution it is a descriptive measure of variation used for interpretation with reference to any statistic. It is also used to infer the sampling variation in a hypothetical universe of homogeneous statistics. Francis Galton (203, p. 57) describes the significance of the term:

> The term Probable Error, in its plain English interpretation of the *most* Probable Error, is quite misleading, for it is *not* that. The most Probable Error (as Dr. Venn has pointed out, in his Logic of Chance) is zero.
>
> It is astonishing that mathematicians, who are the most precise and perspica-

cious of men, have not long since revolted against this cumbrous, slip-shod, and misleading phrase. They really mean what I should call the Mid-Error, but their phrase is too firmly established for me to uproot it. I shall, however, always write the word Probable when used in this sense, in the form of "Prob."; thus "Prob. Error," as a continual protest against its illegitimate use, and as some slight safeguard against its misinterpretation.

D. Presentation and preservation of original data. Those who use statistics are at the mercy of the author who publishes his results. A considerable proportion of physiologists publish the constants which they compute from their data but omit the publication of original observations. Other workers in the subject who approach similar problems from slightly different viewpoints frequently find it impossible to make use of such material.

There are some investigators who deprecate the publication of original observations, because they believe that the scientific opinion of the individual experimenter is the only thing which counts.

This attitude of mind interferes with physiological progress. Several factors make the preservation of raw data of prime importance. First, data collected for one purpose very frequently can be applied by other subsequent workers for the solution of entirely different problems. Second, many problems involving broad generalizations could never be solved by the data which any one investigator, or any one group of investigators are able to collect. Third, since no physiological phenomenon is static, all information regarding long time trends would be lost by maintaining this attitude. Fourth, opinions and conclusions are always transitory while data accumulated under known conditions are comparatively absolute in character. It is an unusually fine piece of physiological work in which the opinions of the author maintain their soundness for a period of 25 to 50 years. On the other hand, the data of almost any laboratory worker, if he conscientiously describes his technique and material, have considerable value for an indefinite period.

Clearly it is the duty of physiologists to preserve their original observations. The question of ways and means then comes up for consideration. At the present time the bulk of such original data could be published by physiological journals with slight added expense. If raw data become too bulky to be printed on one or two pages, publication by photographic means can be used. This subject is adequately discussed by Albrecht (7) and by Livingston (340). An example of its application is seen in an article by Dunn (135, p. 446). He reproduces 18 numerical observations upon each of 478 individuals *in one plate.*

The correlation tables necessary to have given approximately the same amount of information would have taken up 92 pages. Very few physiological problems involve data too extensive to be photographically published. When original data of large studies cannot be published, they should be preserved in some central deposit. The Wistar Institute furnishes such a service for anatomical data. The British Association (99) took a definite stand on this necessary matter. "Negotiations with the Natural History Museum at South Kensington and with the Royal Society of Edinburgh have resulted in the establishment of the required archives for the reception of biological data, where they will be available to students, and in this sense will have secured effective publication."

The necessity for publication of raw data should not be confused with publication of constants computed from these data. The tendency is to over-publish the number of constants which are necessary in the presentation of a physiological paper. After all, if an investigator publishes a description of his technique, his material, his original data, the steps he took in analysis, and then gives his general conclusions, the entire story is told.

E. Analysis of mass data. Thus far the discussion of the application of statistical method to physiology has been directed at its use in connection with laboratory and experimental work. The usual concept of a statistical study is one which involves large quantities of data and elaborate biometric procedures. As a matter of fact the use of statistical method in laboratory work and its employment in the analysis of mass data is based on the same fundamental concept. Samples are used to estimate the probable character of the universe from which they are drawn. When samples are small as in most laboratory problems it is more necessary to evaluate by means of probable error the uncertainty of those judgments which concern the universe. When samples are large as in mass analysis the necessity for the use of probable error is minimized because the universe is already adequately comprehended. In both situations the investigator desires a description which will yield the truth about the phenomena which are being studied, a description which will not vary due to sampling but which truly represents the order of things as they exist.

A statistical description built upon homogeneous mass data is something different than any or all of its constituent parts considered as individuals. Such a quantitative description might be termed a physiological entity. An entity is conceived as an actuality only in so far as

it has probability of occurrence as a potential or actual homogeneity in time or space.

An entity is proved to be a new concept if it functions in a new and different manner than does any of its constituent elements.

For instance, the nerve cell can be considered as an entity of cellular structure; the nervous system, made up of many nerve cells, is a new and different entity with functions unlike its individual elements. A statistical observation on the growth of single individuals is something quite different from the abstract concept of growth arising from a mass study of many growing individuals. The picture of influenza death in the individual will not lead to the entirely different concept of an influenza epidemic entity. Physiology as a subject differs from pathology, anatomy, and biological chemistry primarily because it studies the body of man and animal as entities. Mass analyses of data lead to concepts of statistical entities which, as mass concepts, are distinct from their integral elements and possess peculiar characteristics of their own. From a study of such statistical entities on a broad scale will come the discovery of some of the fundamental laws of physiology, biology, growth and disease.

The realization and description of physiological entities is the goal of quantitative physiology. It is difficult to see how such a goal could be achieved without statistical methods since the entity is pictured only in terms of probabilities.

An essential step to be taken before such entities can be satisfactorily defined is the formulation of normal standards. The laboratory worker constantly emphasizes the necessity for controls in the interpretation of his experiments. The same investigator is willing to overlook the same kind of need for a statistical norm relative to quantitative data. The place where adequate statistical norms are particularly necessary is in the application of physiological tests to clinical medicine. A normal standard for physiological tests used in medicine should have the following characteristics:

1. It should involve a representative group of people whose basic characteristics such as sex, age, race, disease history, occupational and social environment, are recorded and who truly represent as near as possible a cross-section of the locality in which the standard is going to be used.
2. It should be established on large numbers of individuals.
3. It should consist of records homogeneous with respect both to

observers and technical methods. The physiological technique used should be stated in detail.

4. It should always involve reference to time, by year, month, day and hour.

5. It should be published in some manner which makes it universally available.

6. A normal standard of this type should be reëstablished periodically in order to correct for time trend.

The formation of such a norm would have the following effects:

1. It would permit comparison of a great variety of physiological entities with reference to a common standard.

2. It would cut down to a very large degree the number of observations necessary to prove the significance of differences between physiological entities and the normal values.

3. It would facilitate the comparison of physiological findings from one geographical section of the country to those of another.

4. It would introduce consideration of long time trend which would result in a dynamic rather than a static description of physiological entities.

SUMMARY

Statistical method is a scientific tool which can be readily adopted for the analysis of physiological data. It is useful as a laboratory aid to an unbiased, critical attitude. It describes in an adequate and simple way a mass of complicated data. It helps in testing the reliability of technique. It measures significance of experimental results. It evaluates the experimental control. It holds constant factors which otherwise would have to be considered as experimental variables. It measures differences between kinds of constants or descriptive terms and tells the degree of such differences. It helps in generalization of physiological results by evaluating the likelihood of variations due to sampling. It brings together and describes the degree of relationship between widely different kinds of variables. It opens up the possibility of mass analysis in a great variety of physiological data with the resultant prospect of defining broad general physiological laws.

APPENDIX I

Glossary of Symbols Used in Statistical Methods

Greek Alphabet

A	α	Alpha	N	ν	Nu
B	β	Beta	Ξ	ξ	Xi
Γ	γ	Gamma	O	o	Omicron
Δ	δ	Delta	Π	π	Pi
E	ϵ	Epsilon	P	ρ	Rho
Z	ζ	Zeta	Σ	σ	Sigma
H	η	Eta	T	τ	Tau
Θ	θ	Theta	Υ	υ	Upsilon
I	ι	Iota	Φ	φ	Phi
K	κ	Kappa	X	χ	Chi
Λ	λ	Lambda	Ψ	ψ	Psi
M	μ	Mu	Ω	ω	Omega

Common Mathematical Symbols

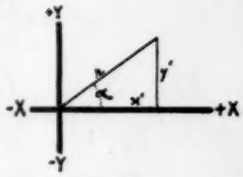
$\pm$	plus or minus
$\div$	divided by
.	multiplied by, if between variables; decimal point, in number; holding as constant factors, if in the subscripts of partial correlation or σ
$=$	equals
$\neq$	does not equal
$\fallingdotseq$	equals approximately
$\doteq$	approaches
$<$	less than
$>$	greater than
$\therefore$	therefore
$\sqrt{n} = \sqrt[2]{n} = n^{\frac{1}{2}}$	square root of n
$\sqrt[m]{n} = n^{\frac{1}{m}}$	m^{th} root of n
$\underline{n} = n!$	factorial $n = (n)\ (n-1)\ (n-2)\ldots\ldots (n-(n-1))$
$\int$	sign of integration, summation sign used in calculus
$\int_b^a$	integration between the limits b and a
∞	infinity
Σ	sum of
$e = \epsilon$	2.171828 unless otherwise stated
π	3.141593 unless otherwise stated
log	common or Briggsian logarithm to base 10
$\log_e$	natural, hyperbolic or Naperian logarithm to base e
a^n	the constant a raised to n^{th} power
$a^{-n} = \frac{1}{a^n}$	the constant a raised to minus n^{th} power
Δy	increment or finite increase in variable y

Common Mathematical Symbols—*continued*

dy	differential of y
$\frac{dy}{dx}$	derivative of $y = f(x)$ with respect to x
$\frac{d^n y}{dx^n}$	n^{th} derivative of $y = f(x)$ with respect to x
$\frac{\partial x}{\partial y}$	partial derivative of x with respect to y
$f(x)$, $\varphi(x)$, $F(x)$	symbols for functions of x
x_1, x_2, x_a (etc.)	subscripts (such as 1, 2, and a) to any constant or variable name the condition described by the constant or variable

Trigonometric Functions

$\sin \alpha$	sine α =	y'/r	in figure
$\cos \alpha$	cosine α =	x'/r	" "
$\tan \alpha$	tangent α =	y'/x'	" "
$\cot \alpha$	cotangent α =	x'/y'	" "
$\sec \alpha$	secant α =	r/x'	" "
$\csc \alpha$	cosecant α =	r/y'	" "
$\text{vers } \alpha$	versine α =	$1 - x'/r$	" "
$\text{covers } \alpha$	coversine α =	$1 - y'/r$	" "



$\sin^{-1} \alpha$	anti-sin α; or an angle whose sine is α
$\sinh \alpha$	hyperbolic sine $\alpha = \frac{1}{2}(e^{\alpha} - e^{-\alpha})$
$\sinh^{-1} \alpha$	an angle whose hyperbolic sine is α

Frequency Distributions

General Terms

x or X abscissa; y or Y ordinate	any letter near the end of alphabet may be used to indicate a variable quantity, but most commonly x and y are used
$\bar{x}$ or $\bar{y}$	deviation of x or y values from arithmetic mean of x or y
$\overline{X}$ or $\overline{Y}$	arithmetic mean x and y
N or n	total frequency, number of observations, any constant
Z	frequency in class intervals
$w_1\, w_2\, w_3$	weights attached to a series of measures being averaged
p	probability of an event happening = $1 - q$
q	probability of an event not happening = $1 - p$
$\chi_1 = \frac{0.67449}{\sqrt{n}}$	tabled in 478 (bibliography)
$\chi_2 = \frac{0.67449}{\sqrt{2n}}$	tabled in 478 (bibliography)

Frequency Distributions —*continued*

Central Tendency Statistics

M	arithmetic average, average, arithmetic mean, mean
M_d	median
M_o	mode
M_g	geometric mean
M_h	harmonic mean
D	distance between and mode

$\nu_1, \nu_2, \nu_3, \nu_4$	moments of a frequency distribution about arbitrary origin
$\pi_1, \pi_2, \pi_3, \pi_4$	moments of a frequency distribution about arithmetic mean without Sheppard's corrections
$\mu_1, \mu_2, \mu_3, \mu_4$	moments of a frequency distribution about arithmetic mean with Sheppard's corrections
σ	standard deviation; root arithmetic mean square deviation
S	root mean square deviation about an origin other than arithmetic average

Statistics of Variation

P.E.	probable error
V	coefficient of variation expressed as unity
C.V.	coefficient of variation expressed in per cent
q_1	the lower quartile
q_3	the upper quartile
q	semi-interquartile range
β_1	μ_3^2/μ_2^3
β_2	μ_4/μ_2^2
$\lambda = sk =$	skewness coefficient
κ	kappa, a criterion of curve type used by Pearson and calculated in terms of β_1 and β_2
ψ	psi $= \text{C.V.} \left[1 + 2\left(\frac{\text{c.v.}}{100}\right)^2\right]^{1/2}$ tabled in 478 (bibliography)

Correlation and Contingency

r	correlation coefficient
η	eta, correlation ratio
R	multiple correlation coefficient
R_s	a measure of correlation by ranks found by Spearman's "Footrule"
r_s	correlation coefficient determined from R_s
r_t	correlation coefficient calculated from fourfold table; tetrachoric correlation

Correlation and Contingency —*continued*	C	coefficient of contingency
	φ	mean square contingency
	χ^2	Chi square, a measure used in testing goodness of fit and presence of association
	In equations fitted to observed data	The letters $a, b, c, d, e, f, g, h, i, j, k$, are used as constants
		The letter b in linear equations signifies the rate of increase
		The letters u, v, w, x, y, z, are used to indicate variables

APPENDIX II

TABLE OF EQUATIONS IN COMMON STATISTICAL USE

A. Table of Constants

	Symbol	*Number*	*Logarithm*
Base of hyperbolic (natural) logarithms	e	2.7182818	0.43429448
Reciprocal of e	$1/e$	0.36787945	9.5657055–10
Modulus of common system of logarithms	$\log_e$	0.43429448	9.6377843–10
Reciprocal of modulus	$1/\log_e$	2.3025851	0.3622157
Ratio of circumference to diameter of circle	π	3.1415927	0.4971499
Reciprocal of π	$1/\pi$	0.3183099	9.5028501–10
Square root of π	$\sqrt{\pi}$	1.7724538	0.2485749
Reciprocal of square root of π	$1/\sqrt{\pi}$	0.5641896	9.7514251–10
Square root of 2π	$\sqrt{2\pi}$	2.506628	0.399090
Reciprocal of square root of 2π	$1/\sqrt{2\pi}$	0.3989422	9.6009101–10
Probable error ÷ standard deviation (T)	T	0.6744898	9.828976–10
Reciprocal of T	$1/T$	1.4826021	0.1710246

B. Formulae and Probable Errors for Frequency Distributions (see page 336).

C. Formulae and Probable Errors for Multiple Variants (see page 339).

D. Equations for Translation of Moments and Sheppard's Corrections

Without Sheppard's corrections	(mean): $\pi_1 = \nu_1 +$ arbitrary origin	
	(Standard deviation squared): $\pi_2 = \nu_2 - (\nu_1)^2$	
	(Third moment about mean): $\pi_3 = \nu_3 - 3\nu_1\nu_2 + 2\nu_1^3$	
	(Fourth moment about mean): $\pi_4 = \nu_4 - 4\nu_1\nu_3 + 6\nu_1^2\nu_2 - 3\nu_1^4$	

D. Equations for Translation of Moments—continued

Sheppard's corrections	(Mean): $\mu_1 = \pi_1$
	(Standard deviation squared): $\mu_2 = \pi_2 - \frac{1}{12}$
	(Third moment about mean): $\mu_3 = \pi_4$
	(Fourth moment about mean): $\mu_4 = \pi_4 - \frac{1}{2}\pi_2 + \frac{7}{240}$
	Cross product moment: $\mu_{xy} = \nu_{xy} - \nu_x \nu_y$

E. Functional Relations of $y = f(x_1, x_2, \ldots\ldots x_n)$

FUNCTION	MEANS	STANDARD DEVIATION
$y = x_1 + x_2$	$M_1 + M_2$	$[\sigma_1^2 + \sigma_2^2 + 2\, r_{12}\, \sigma_1\, \sigma_2]^{\frac{1}{2}}$
$y = x_1 + x_2 + x_3$	$M_1 + M_2 + M_3$	$[\sigma_1^2 + \sigma_2^2 + \sigma_3^2 + 2\, r_{12}\, \sigma_1\, \sigma_2 + 2\, r_{13}\, \sigma_1\, \sigma_3 + 2\, r_{23}\, \sigma_2\, \sigma_3]^{\frac{1}{2}}$
$y = x_1 - x_2$	$M_1 - M_2$	$[\sigma_1^2 + \sigma_2^2 - 2\, r_{12}\, \sigma_1\, \sigma_2]^{\frac{1}{2}}$
$y = x_1 \cdot x_2$	$M_1 M_2 + r_{12}\, \sigma_1\, \sigma_2$	$M_1 M_2\, [V_1^2 + V_2^2 + 2 r_{12} V_1 V_2 + V_1^2 V_2^2 (1 + r_{12})]^{\frac{1}{2}}$ or approximately $M_1 M_2\, [V_1^2 + V_2^2 + 2\, r_{12}\, V_1\, V_2]^{\frac{1}{2}}$
$y = x_1 \cdot x_2 \cdot x_3$	$M_1 M_2 M_3\, [1 + r_{12}\, V_1\, V_2 + r_{13}\, V_1\, V_3 + r_{23}\, V_2\, V_3]$	$M_1\, M_2\, M_3\, [V_1^2 + V_2^2 + V_3^2 + 2\, r_{12}\, V_1\, V_2 + 2\, r_{13}\, V_1\, V_3 + 2\, r_{23}\, V_2\, V_3]^{\frac{1}{2}}$ approximately
$y = \frac{x_1}{x_2}$	$\frac{M_1}{M_2}(1 + V_2^2 - r_{12}\, V_1\, V_2)$	$\frac{M_1}{M_2}\, [V_1^2 + V_2^2 - 2\, r_{12}\, V_1\, V_2]^{\frac{1}{2}}$
$y =$ any function x	(See bibliography, 117 and 503)	(See bibliography, 117 and 503)

In above equations V signifies coefficient of variation in terms of unity $\therefore \frac{\sigma}{M}$. The various r values are correlation coefficients between errors and ordinarily can be considered to be zero (see p. 324). When not zero and if frequencies are involved, they can be computed by equation: $r_{y_1 y_2} = -\frac{1}{n}\left(\frac{y_1\, y_2}{\sigma_{y1}\, \sigma_{y2}}\right)$. See bibliography, 308 (p. 153).

F. Frequency Equations in Common Use

Normal curve	$y = \frac{n}{\sqrt{2\pi}\,\sigma} e^{-\frac{1}{2}\left(\frac{\bar{x}}{\sigma}\right)^2} = 0.47694 \frac{n}{\sqrt{\pi}\,\mathrm{PE}} e^{-0.227468\left(\frac{\bar{x}}{\mathrm{PE}}\right)^2}$
	Maximum $y = 0.39894 \frac{n}{\sigma} = 0.26908 \frac{n}{\mathrm{P.E.}}$
	$\sigma = 1.48260$ P.E.
	PE $= 0.67449\,\sigma$
	$n = 2.5066$ (maximum y)$\sigma = 3.7163$ (maximum y) (P.E.)
	The probability integral is given in 513 (p. 14)
Normal correlation surface	$y = \frac{n}{2\pi\sigma_1\sigma_2\sqrt{1-r_{12}^2}} e^{-\frac{1}{2}\left(\frac{\bar{x}_1^2}{\sigma_{1.2}^2} + \frac{\bar{x}_2^2}{\sigma_{2.1}^2} - 2r_{12}\frac{\bar{x}_1\bar{x}_2}{\sigma_{1.2}\sigma_{2.1}}\right)}$
Skew Frequency curves Pearson	Best described with examples in 164, equations being summarized on page 47
Skew Frequency curves Gram-Charlier	Summarized in 180, 181, and 514 (pp. 156–172)

B. Formulae and Probable Errors for Frequency Distributions

NAME	FORMULAE	PROBABLE ERROR FORMULAE	CONDITIONS FOR USE OF PROBABLE ERROR FORMULAE*
Arithmetic Mean — Numerical Average	$\frac{\Sigma(x)}{n}$	$\pm 0.6745\left(\frac{\sigma}{\sqrt{n-1}}\right)$	A, C, E, H
Arithmetic Mean — Proportionate Average — In terms of unity	$p = 1 - q = \frac{n_1}{n_1 + (n - n_1)}$	$\pm 0.6745\sqrt{\frac{p \cdot q}{n}}$	A, C, E, (interpret size of n relative to p and q, see page 309)
Arithmetic Mean — Proportionate Average — Expected number	np	$\pm 0.6745\sqrt{n \cdot p \cdot q}$	
Geometric Mean (Mg)	$\text{anti log}\left[\frac{\Sigma(\log x)}{n}\right]$		
Harmonic Mean (Mh)	$\frac{n}{\Sigma\left(\frac{1}{x}\right)}$		
Weighted Mean (Mw)	$\frac{\Sigma(w \cdot x)}{\Sigma w}$		
Median (Md)	mid point of a distribution arranged in order of magnitude	$\pm 0.84535\left(\frac{\sigma}{\sqrt{n}}\right)$	A, G
		± 1.25332 (P.E. of mean)	
Distance between Mean and Theoretical Mode (D)	$(sk)\,\sigma$	$\pm 0.6745\sigma\sqrt{\frac{3}{2n}}$	A, D, F
		(See bibliography, 478, p. lxxii)	B, C

Theoretical Mode (Mo.)	mean $- D$	$\pm \sqrt{(\text{P.E.}_D)^2 + (\text{P.E.}_M)^2}$	A, G
Empirical Mode	mean $-$ 3 (mean-median)		
Range	difference between highest and lowest case	(see bibliography, 434, 609)	
Standard Deviation (σ)	$\sqrt{\frac{\Sigma(\bar{x})^2}{n}}$	$\pm 0.6745\left(\frac{\sigma}{\sqrt{2\,(n-1)}}\right) = \chi\sigma$	A, C, F, H
		$\pm 0.6745\sqrt{\frac{\mu_4 - \mu_2{}^2}{4\mu_2 \cdot n}}$	B, C, E
Average or Mean Deviation	$\frac{\Sigma\bar{x}}{n}$ [treating all deviations as positive]		
Quartile Deviation	q_1 or q_3	$\pm 0.9191\left(\frac{\sigma}{\sqrt{n}}\right)$	A, D, F
Semi-interquartile Range (q)	$q_3 - q_1$	$\pm 0.5306\left(\frac{\sigma}{\sqrt{n}}\right)$	A, D, F
Coefficient of Variation (c.v.)	$100\left(\frac{\sigma}{m}\right)$	$\pm 0.6745\left(\frac{\text{c.v.}}{\sqrt{2(n-1)}}\right)\left[1 + 2\left(\frac{\text{c.v.}}{100}\right)^2\right]^{\frac{1}{2}} = \chi^2\psi$	A, C, F
Any Observed Frequency Group (y_1)	$\frac{y_1}{n}$	$\pm 0.6745\sqrt{y_1\left(1 - \frac{y_1}{n}\right)}$	A, C, E
Second moment about mean π_2	$[\nu_2 - (\nu_1)^2]$	$\pm 0.6745\,\sigma^2\sqrt{\frac{2}{n}}$	A, C, F
Third moment about mean π_3	$\nu_3 - 3\nu_1\nu_2 + 2\nu_1{}^3$	$\pm 0.6745\,\sigma^3\sqrt{\frac{6}{n}}$	A, C, F

NAME	FORMULAE	PROBABLE ERROR FORMULAE	CONDITIONS FOR USE OF PROBABLE ERROR FORMULAE*
Fourth moment about mean π_4	$\nu_4 - 4\nu_1\nu_3 + 6\nu_1^2\nu_2 - 3\nu_1^4$	$\pm 0.6745\,\sigma^4\sqrt{\frac{96}{n}}$	A, C, F
Beta one (β_1)	$\frac{\mu_3^2}{\mu_2^3}$	See bibliography, 478, p. lxv	B, C, F
Beta two (β_2)	$\frac{\mu_4}{\mu_2^2}$	See bibliography, 478, p. lxv	B, C, F
Skewness ($sk.$ or λ)	$\frac{\sqrt{\beta_1}\,(\beta_2+3)}{2\,(5\beta_2 - 6\beta_1 - 9)}$	See bibliography, 478, p. lxv	B, C, F
Kappa one (κ_1)	$2\beta_2 - 3\beta_1 - 6$	See bibliography, 478, p. lxii	B, C, F
Kappa two (κ_2)	$\frac{\beta_1\,(\beta_2+3)^2}{4\,(4\beta_2 - 3\beta_1)\,(2\beta_2 - 3\beta_1 - 6)}$	See bibliography, 478, p. lxii	B, C, F
Kurtosis	$\beta_2 - 3$	Same as P.E.$_{\beta_2}$	B, C, F

* Principal conditions for use of probable error formulae:

A. Satisfactory to use probable error formulae if the observed sample comes from a hypothetical infinite, normal distribution of such samples.

B. Satisfactory to use probable error formulae if the observed sample arises from a hypothetical infinite distribution of such samples, whose characteristics are defined by β_1 and β_2.

C. Satisfactory probable error formulae if n is large, regardless of type of distribution of sampled constants.

D. Satisfactory probable error formulae if n is large and there is a normal distribution of sampled constants.

E. Satisfactory probable error formulae if n is small regardless of type of distribution of sampled constants.

F. Satisfactory probable error formulae if n is small and normal distribution of sampled constants.

G. Probable error formulae is satisfactory if it is interpreted within larger boundaries of significance than ordinarily used.

H. N, or total number of observations, is corrected for the number of limitations in degrees of freedom.

I. Regression of means is assumed to be essentially linear.

C. Formulae and Probable Errors for Multiple Variants

NAME	FORMULAE	PROBABLE ERROR FORMULAE	CONDITIONS FOR USE OF PROBABLE ERROR FORMULAE*
Correlation Coefficient (r)	$\dfrac{\Sigma(\bar{x}\,\bar{y})}{n\,\sigma_x\,\sigma_y}$	$\pm 0.6745\left[\dfrac{(1-r^2)}{\sqrt{n}}\right]$	A, C, F, I
	$\dfrac{\nu_{xy}-\nu_x\cdot\nu_y}{\sqrt{\nu_{2x}-(\nu_{1x})^2}\sqrt{\nu_{2y}-(\nu_{1y})^2}}$	$\pm 0.6745\left[\dfrac{(1-r^2)}{\sqrt{n-2}}\right]$	A, C, F, H, I
	$\dfrac{\mu_{xy}}{\sqrt{\mu_{2x}}\sqrt{\mu_{2y}}}$		
Partial Correlation Coefficient $r_{12\,34\ldots n}$**	$\dfrac{r_{12.34\ldots(n-1)}-[r_{1n.34\ldots(n-1)}]\,[r_{2n.34\ldots(n-1)}]}{[1-r^2_{1n.34\ldots(n-1)}]^{\frac{1}{2}}\,[1-r^2_{2n\,34\ldots(n-1)}]^{\frac{1}{2}}}$	$\pm 0.6745\dfrac{[1-r^2_{12.34\ldots n}]}{\sqrt{n-k}}$	A, C, F, H, I
Multiple Correlation Coefficient (R)**	$1-R^2_{1(23\ldots n)}=$ $(1-r^2_{12})\,(1-r^2_{13.2})\,(1-r^2_{14.23})\ldots(1-r^2_{1n.23\ldots(n-1)})$	$\pm 0.6745\dfrac{[1-R^2_{1\,(23\ldots n)}]}{\sqrt{n-k}}$	A, C, F, H, I
y as computed from	$y=\overline{Y}+r_{xy}\dfrac{\sigma_y}{\sigma_x}(x-\overline{X})$	$\pm 0.6745\,\sigma_y\sqrt{1-r^2_{xy}}$	A, C, F, I
x as computed from	$x=\overline{X}+r_{xy}\dfrac{\sigma_x}{\sigma_y}(y-\overline{Y})$	$\pm 0.6745\,\sigma_x\sqrt{1-r^2_{xy}}$	A, C, F, I
Regression Coefficients	$r_{xy}\dfrac{\sigma_y}{\sigma_x}$	$\pm 0.6745\sqrt{\dfrac{1-r^2_{xy}}{n-2}}\left[\dfrac{\sigma_y}{\sigma_x}\right]$	A, C, F, H, I
	$r_{xy}\dfrac{\sigma_x}{\sigma_y}$	$\pm 0.6745\sqrt{\dfrac{1-r^2_{xy}}{n-2}}\left[\dfrac{\sigma_x}{\sigma_y}\right]$	A, C, F, H, I

NAME	FORMULAE	PROBABLE ERROR FORMULAE	CONDITIONS FOR USE OF PROBABLE ERROR FORMULAE*
Standard deviation about regression lines	$\sigma_{x.y} = \sqrt{(\sigma_x)^2 (1 - r_{xy}^2)}$	$\pm 0.6745 \frac{\sigma_{x.y}}{\sqrt{2(n-2)}}$	A, C, F, H, I
	$\sigma_{y.x} = \sqrt{(\sigma_y)^2 (1 - r_{xy}^2)}$	$\pm 0.6745 \frac{\sigma_{y.x}}{\sqrt{2(n-2)}}$	A, C, F, H, I
Any partial standard deviation**	$\sigma_{1.23\ldots n} = \sqrt{(\sigma_1)^2 (1 - r_{12}^2)(1 - r_{13.2}^2)\ldots(1 - r_{1n.23\ldots(n-1)}^2)}$	$\pm 0.6745 \frac{\sigma_{1.234\ldots n}}{\sqrt{2(n-k)}}$	A, C, F, H, I
Correlation ratio, eta, η	$\eta_{xy} = \left[\frac{\Sigma\,[n \text{ in each array } (M_{\text{array}} - M_y)^2]}{n\,\sigma_y^2}\right]^{\frac{1}{2}}$	$\pm 0.6745 \left[\frac{1-\eta^2}{\sqrt{n-2}}\right]$	A, D, F, H
Test for linearity	$(\eta^2 - r^2)$	$\pm 1.349 \sqrt{\frac{\eta^2 - r^2}{n-2}} \sqrt{(1-\eta^2) - (1-r^2)^2 + 1}$	A, D, F, G, H
Tetrachoric $r(r_t)$	(See bibliography, 478)	(See bibliography, 478)	A, D, F
Mean Square Contingency (ϕ^2)	$\frac{\chi^2}{n}$	(See bibliography, 466a)	A, D
Coefficient of Contingency (c)	$\sqrt{\frac{\phi^2}{1+\phi^2}} = \sqrt{\frac{\chi^2}{n+\chi^2}}$	(See bibliography, 466a)	A, D
Spearman's foot rule for rank correlation	$R_s = 1 - \frac{6\Sigma\,(\text{gains})}{n^2 - 1}$	(See bibliography, 460)	
	$r_s = 2\cos\frac{\pi}{3}(1 - R_s) - 1$		

* See footnote Appendix II, B (page 338).

** k is constant introduced to correct for limitation in degrees of freedom. For zero order correlation k is 2; for zero order standard deviation k is 1; for each higher order of correlation or standard deviation k is increased by one.

APPENDIX III

Tables and Figures of Probability Functions

Proportionate Area under Normal Curve Beyond $\pm \frac{\bar{x}}{\sigma}$ Limits when Total Area under Normal Curve is Unity.

Note: $\bar{x}$ deviation from mean and σ, the standard deviation; $\bar{x}$ and σ must be measured in similar units.

$\frac{\bar{x}}{\sigma}$	AREA	$\frac{\bar{x}}{\sigma}$	AREA	$\frac{\bar{x}}{\sigma}$	AREA	$\frac{\bar{x}}{\sigma}$	AREA	$\frac{\bar{x}}{\sigma}$	AREA	$\frac{\bar{x}}{\sigma}$	AREA
0.00	1.000	0.24	0.810	0.58	0.562	0.92	0.358	1.50	0.134	2.4	0.016
0.01	0.992	0.26	0.795	0.60	0.549	0.94	0.347	1.55	0.121	2.5	0.012
0.02	0.984	0.28	0.779	0.62	0.535	0.96	0.337	1.60	0.110	2.6	0.0093
0.03	0.976	0.30	0.764	0.64	0.522	0.98	0.327	1.65	0.099	2.7	0.0069
0.04	0.968	0.32	0.749	0.66	0.509	1.00	0.317	1.70	0.089	2.8	0.0051
0.05	0.960	0.34	0.734	0.68	0.497	1.02	0.308	1.75	0.080	2.9	0.0037
0.06	0.952	0.36	0.719	0.70	0.484	1.04	0.298	1.80	0.072	3.0	0.0027
0.07	0.944	0.38	0.704	0.72	0.472	1.06	0.289	1.85	0.064	3.1	0.0019
0.08	0.936	0.40	0.689	0.74	0.459	1.08	0.280	1.90	0.057	3.2	0.0014
0.09	0.928	0.42	0.674	0.76	0.447	1.10	0.271	1.95	0.051	3.4	0.00067
0.10	0.920	0.44	0.660	0.78	0.435	1.15	0.250	2.00	0.046	3.6	0.00032
0.12	0.904	0.46	0.646	0.80	0.424	1.20	0.230	2.05	0.040	3.8	0.00014
0.14	0.889	0.48	0.631	0.82	0.412	1.25	0.211	2.10	0.036	4.0	0.000063
0.16	0.873	0.50	0.617	0.84	0.401	1.30	0.194	2.15	0.032	4.5	0.000,007
0.18	0.857	0.52	0.603	0.86	0.390	1.35	0.177	2.20	0.028	5.0	0.000,000,6
0.20	0.841	0.54	0.589	0.88	0.379	1.40	0.162	2.25	0.024	5.5	0.000,000,04
0.22	0.826	0.56	0.575	0.90	0.368	1.45	0.147	2.30	0.021	6.0	0.000,000,002

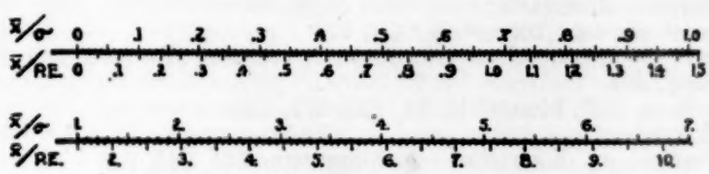


Fig. 5. Nomogram for computing $\frac{\bar{x}}{\sigma}$ from $\frac{\bar{x}}{\text{P.E.}}$

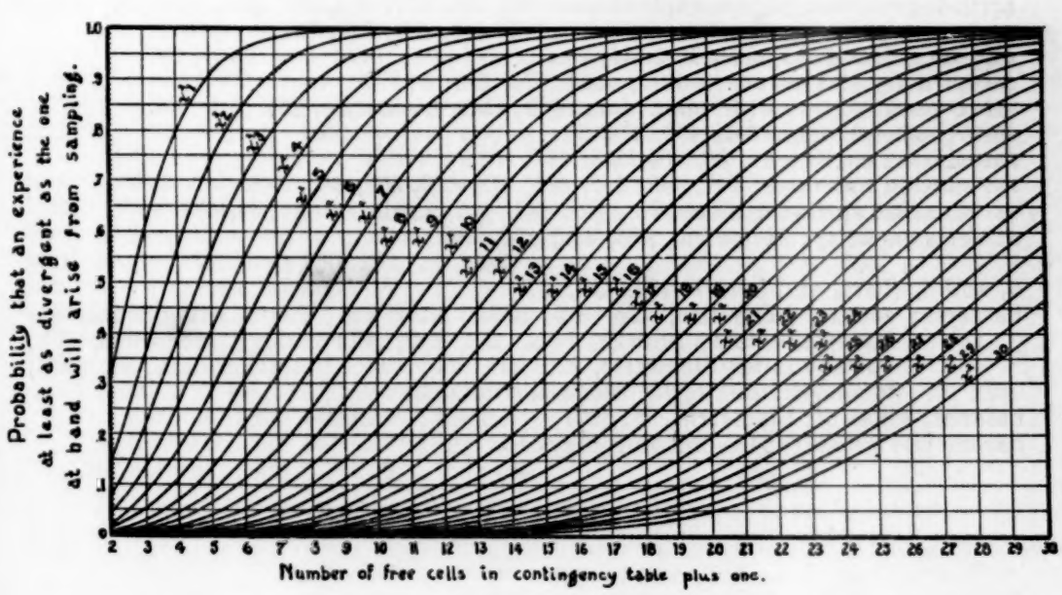

Probability that an experience at least as divergent as the one at hand will arise from sampling.
Number of free cells in contingency table plus one.

Fig. 6. Nomogram for computing probability equivalent from values of χ^2. In entering this table, n = number of free cells + one = (number of rows minus one) (number of columns minus one) + one.

APPENDIX IV

Cross Index to Bibliography

An adequate review of quantitative physiology involves a survey of what has been accomplished in the subject. Since quantitative physiology merges into borderline studies with a variety of subjects such as anatomy, anthropometry, constitution, pathometry, physiological chemistry, vital statistics, and growth, a complete survey is almost impossible. An attempt is made in the following bibliography to introduce the reader to the more important quantitative works that have been done. Articles or books containing important and more detailed references are listed under "bibliography" in the cross index.

The reference list to statistical articles is particularly sketchy since only those references were selected to which the physiologist would probably like to refer.

The term "data" used in the cross index signifies that considerable numbers of observations have been taken and recorded but no statistical analysis attempted. The term "biometric" implies that either the statistical method or fitted equations have been used in the analysis and in many instances that the original observations are present. "Growth" indicates the growth period, fetal to adult life. "Mathematics of" usually signifies deviation equations of the involved statistical constant or its probable error. "Computation technique" refers to illustrative examples in the computation of statistical constants.

In all instances the numbers in the cross index represent the serial numbers in the bibliography.

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B. Change of ocular characters with age. (i) visual acuity and age; (ii) refraction class and age; (iii) general refraction and age; (iv) general astigmatism and age; (v) corneal refraction and age; (vi) corneal astigmatism and age; (vii) near point and age; (viii) index of sunken eye and age; (ix) interpupillary index and age. Ann. Eugenics, ii, 1927, 111.

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